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Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

OFFICIAL JOURNAL OF AMERICAN THORACIC SOCIETY
MEDICAL SECTION OF THE NATIONAL TUBERCULOSIS ASSOCIATION

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THE AMERICAN REVIEW OF RESPIRATORY DISEASES

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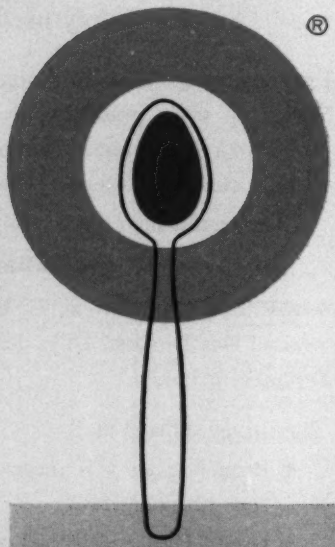

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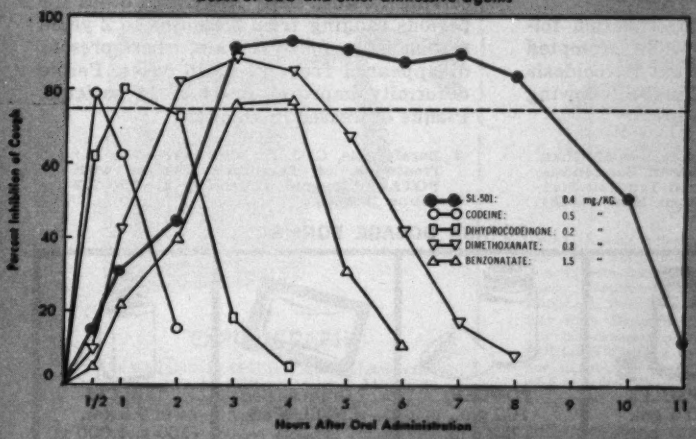

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Chen, J. Y.; Biller, H. F., and Montgomery, E. G., Jr.: J. Pharmacol. & Exper. Therap. *128*:384, 1960.

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1. Cohen, R. V., Lambert, R. L., and Molthan, L.: The Use of POTABA in Sarcoidosis; Annual Meeting American Trudeau Society, Eastern Section, Boston, Mass. (1958).

2. Zarafonetis, C. J. D., and Horrax, T. M.: Treatment of Peyronie's Disease with POTABA, Journal of Urology, 81: 770-772 (June 1959).

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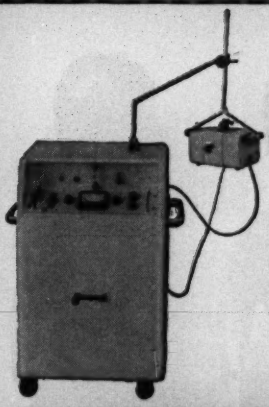

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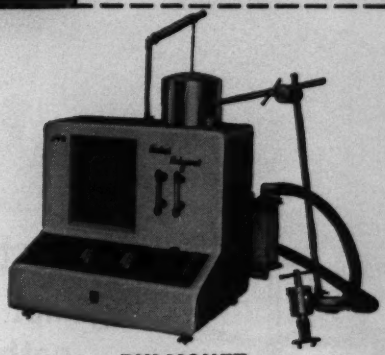

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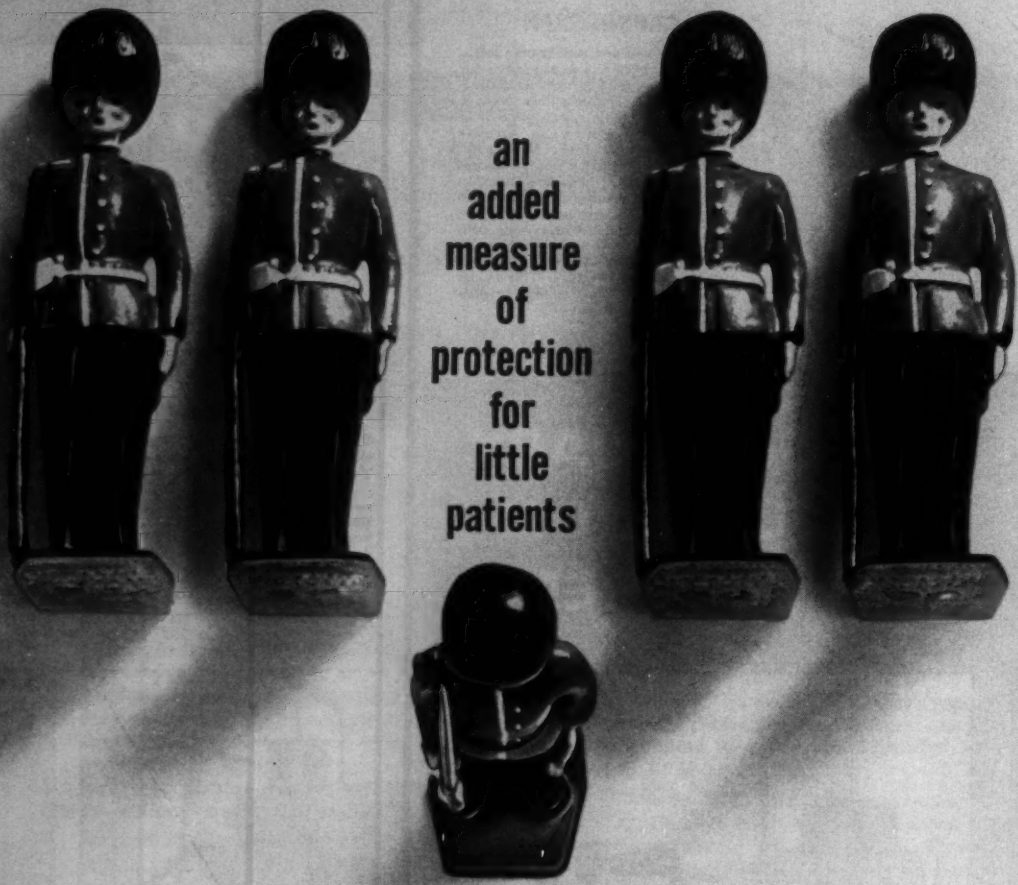

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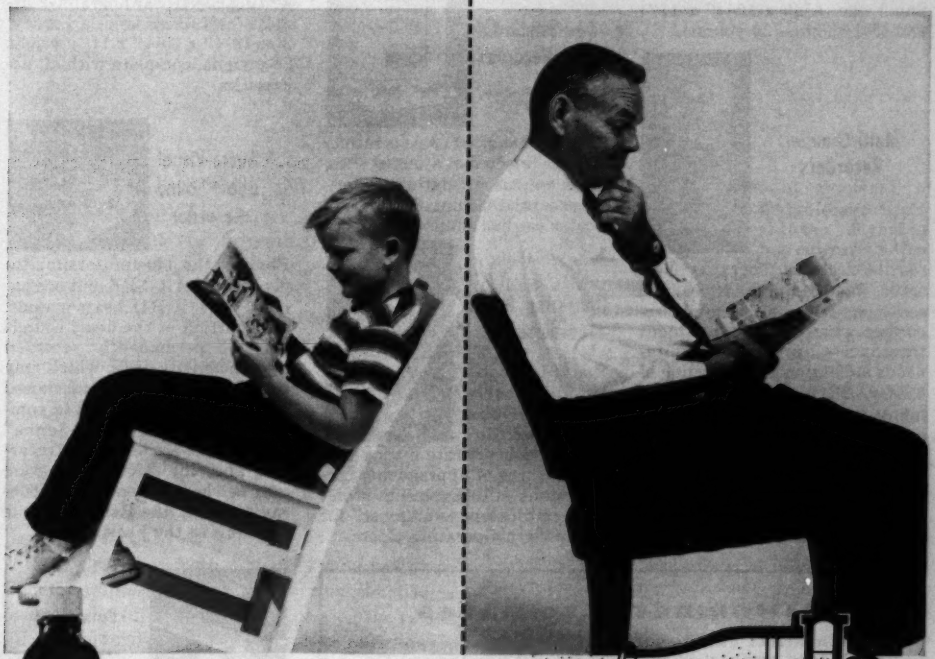

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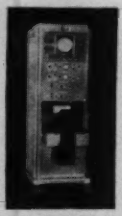

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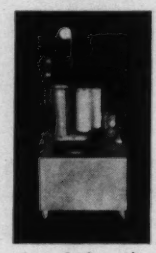

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THE AMERICAN REVIEW
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Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

VOLUME 82 *November 1960* NUMBER 5

THE INFLUENCE OF CHEMOPROPHYLAXIS ON IMMUNITY IN EXPERIMENTAL TUBERCULOSIS[1]

H. P. LAMBERT[2, 3]

(Received for publication May 2, 1960)

Introduction

In recent years much attention has been paid to the possibility of preventing tuberculosis by the use of isoniazid. In unusual circumstances isoniazid may be used in an attempt to prevent infection in tuberculin-negative subjects exposed to special risk, but the usual procedure for such people is to vaccinate them with BCG. More commonly, isoniazid has been used to prevent tuberculous disease in persons who are, judged by the tuberculin test, already infected, but are as yet free from clinical or roentgenographic evidence of disease. The indications for these forms of prophylaxis have been reviewed recently by several authors (1–3).

It is clear that, both in man (4) and in experimental animals (2), isoniazid is very effective in suppressing tuberculous disease during the period of its administration. What remains uncertain is the effect of this procedure on the subject's subsequent immunity against tuberculosis, and on the likelihood of promoting the emergence of isoniazid-resistant strains of bacilli. Whether isoniazid, given to a tuberculin-positive man or animal, interferes with its subsequent immunity, is contingent upon another question: has a subject, infected long enough to have a positive tuberculin reaction, already developed to the fullest extent his resistance to tuberculosis, or does resistance continue to increase over a long period? If resistance goes on building up for a long period, then treatment by isoniazid, although preventing disease while it is given, might leave the subject in a less favorable position with regard to subsequent immunity either to his own remaining bacilli or to exogenous reinfection. On the other hand, if natural acquired resistance is as great as it will ever be within a few weeks of infection, the administration of isoniazid would be less likely to interfere with immunity.

The experiments described were designed to answer the following questions: Does an animal's immunity continue to increase after it has been infected with tuberculosis for a number of weeks, or does immunity reach its maximum soon after infection? Does isoniazid, administered after the animal has already developed antituberculous immunity, interfere with this immunity? Are the surviving bacilli in such animals resistant to isoniazid?

The experiments, like most previous work on this subject, are concerned with isoniazid alone which, being inexpensive, effective, easy to administer, and of low toxicity, is the only drug at present suitable for extensive use as a prophylactic agent.

Plan of Investigation

Materials and Methods

Mycobacterium tuberculosis H37Rv and *M. tuberculosis* Vallée were the strains employed. Both strains were maintained by weekly passage in standard Tween®-albumin medium. Seven-day cultures were used for animal inoculation. The animals used were male albino mice, 18–20 gm., obtained from Carworth Farms, housed in metal cages and fed on pulverized standard mouse pellets with water *ad libitum*. Isoniazid was administered by mixing it with the pulverized pellets

[1] From the Department of Public Health and Preventive Medicine, New York Hospital-Cornell Medical Center, New York, New York.

[2] Dorothy Temple Cross Research Fellow of the Medical Research Council of Great Britain.

[3] Present address: University College Hospital, London, England.

in a McLellan dry batch mixer, to give a final concentration of the drug of 0.003 per cent. This dose gives each mouse a daily dose of 4–5 mg. per kg. of body weight.

Procedure

Immunity was assessed by measuring the ability of tubercle bacilli to multiply in the organs of infected animals. This was done by estimating the actual numbers of bacilli in the spleens and lungs of the animals at various times after a challenge infection. The method was developed by Fenner, Martin, and Pierce (5), and has been described in detail by McCune and Tompsett (6). At suitable times after infection, groups of mice were killed by chloroform. The spleens and lungs were removed by an aseptic technique and emulsions were prepared from these organs with the aid of Teflon homogenizers, the organs being ground in 2 per cent bovine albumin. Dilutions of the homogenates were made in 0.1 per cent bovine albumin and inoculated on the surface of oleic-acid-albumin agar plates. The plates were sealed, incubated at 37°C., and colonies were counted two and four weeks later. From these counts the number of culturable bacilli in the spleen and lungs of each animal was calculated.

Isoniazid susceptibility was tested by inoculating in tubes of Tween-albumin medium containing graded concentrations of isoniazid. A standard strain of H37Rv was always tested in parallel.

Experimental Design

The general design of the experiments is shown in figure 1. A large number of mice of the same age were distributed into six groups, *A* to *F*. *Group A* in each experiment was a control group used for checking the course of the infection after a small primary inoculum of virulent tubercle bacilli. Four mice from this group were killed at four-week intervals after infection, and the bacilli in the spleens and lungs were counted. Mice of *group B* received no infection at the beginning of the experiment, while those of *group C* received the small inoculum of virulent bacilli. A larger challenge dose of virulent bacilli was administered to both *groups B* and *C* eight weeks after the beginning of the experiment, and immunity was estimated by counting the bacilli in the spleens and lungs of 8 to 10 animals from each group at various intervals after challenge. *Groups D*, *E*, and *F* were reserved for later challenge; *group D* consisted of mice which remained uninfected until this challenge, while *groups E* and *F* were both infected with the small primary inoculum. Eight weeks after the beginning of the experiment, mice of *group F* were started on isoniazid. The duration of isoniazid administration varied in different experiments. One or two weeks after isoniazid was discontinued (and four to six months after the beginning of the experiment), a larger challenge dose of bacilli was administered to *groups D*, *E*, and *F*. Immunity was again estimated by counting the bacilli in the spleens and lungs of 8 to 10 animals from each group at various intervals after challenge. Both the small primary inoculum and the larger challenge dose were given by intravenous injection.

In these experiments, immunity was assessed by estimating the degree to which a challenge dose was able to multiply in the animals. Experiments of this general design allowed the following comparisons. The ability of the challenge infection to multiply in *group C* compared with its fate in *group B* gave a measure of any immunity which may have been achieved as a result of the small primary infection eight weeks before challenge. Comparison of *groups D* and *E* determined whether

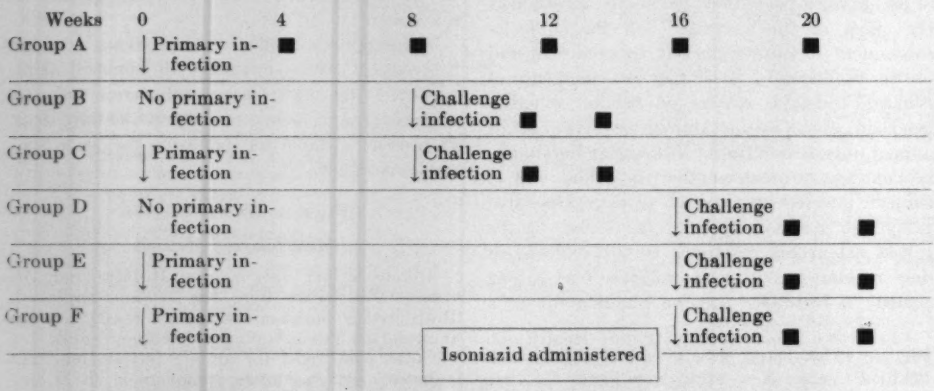

FIG. 1. General design of the experiments.

the immunity resulting from a small primary infection still existed after a further time interval and whether it was different in degree from that found at eight weeks. Comparison of *groups E* and *F* determined whether the administration of isoniazid interfered with the subsequent immunity of the mice to a challenge given after the drug had been discontinued.

Preliminary Experiments with a Low Dose of Isoniazid

Before proceeding to the type of experiment outlined above, it was necessary to confirm the finding of McCune and co-workers (7) that a small dose of isoniazid comparable to that used in the treatment of tuberculosis in man was capable of suppressing experimental tuberculosis in the mouse. The present experiments differed from those of the previous investigators, however, in that a very small inoculum was used, 17 viable units per mouse. Isoniazid was mixed with the food to a final concentration of 0.003 per cent, an amount which gave each mouse a daily dose of isoniazid of about 4 to 5 mg. per kg. of body weight. Mice were maintained on the isoniazid diet from one week before infection until five weeks after infection.

In table 1 the culturable units in the spleens of mice examined at different times after infection

TABLE 1

EFFECT OF ADDITION OF 0.003 PER CENT ISONIAZID TO THE DIET ON POPULATIONS OF M. TUBERCULOSIS H37Rv IN MOUSE SPLEENS. ISONIAZID ADMINISTERED FROM ONE WEEK BEFORE TO FIVE WEEKS AFTER INFECTION. INOCULUM: 17 CULTURABLE UNITS PER MOUSE

Log Culturable Tubercle Bacilli per Spleen	Weeks after Infection				
	2	4	8	12	16
Control group	3.5	5.1	3.6	4.1	3.9
	3.8	5.2	4.9	4.1	2.9
	4.1	3.8	3.9	4.0	4.0
		4.9	4.6	4.0	4.4
		4.4	4.5	3.5	4.4
		4.2	3.5	3.5	4.1
		5.0	4.6	4.0	5.0
Isoniazid group		0	0	5.0	3.8
		0	0	4.8	0
		0	0	0	0
		0	3.5	0	0
		0	0	3.7	3.1
		0	0	4.7	3.5
		0	0	0	3.7
		0	0	0	

Each number is the count from a single spleen.

TABLE 2

EFFECT OF ADDITION OF 0.003 PER CENT ISONIAZID TO THE DIET ON POPULATIONS OF M. TUBERCULOSIS H37Rv IN MOUSE LUNGS. ISONIAZID ADMINISTERED FROM ONE WEEK BEFORE TO FIVE WEEKS AFTER INFECTION. INOCULUM: 17 CULTURABLE UNITS PER MOUSE

Log Culturable Tubercle Bacilli per Lung	Weeks after Infection			
	4	8	12	16
Control group	4.7	2.5	4.3	4.4
	0	4.0	5.1	4.1
	3.2	4.8	4.8	5.2
	3.6	3.9	5.0	5.6
	0	4.9	3.0	5.1
	4.6	4.0	0	5.1
	5.3	0	0	
Isoniazid group	0	0	2.2	4.3
	0	0	2.2	0
	0	0	0	0
	0	0	0	0
	0	0	0	2.7
	0	0	0	2.7
	0	0	0	0
	0	0	0	

Each number is the count from a single lung.

are shown, and the lung counts are shown in table 2. It was evident that this small dose of isoniazid, comparable with that used in human disease, suppressed the infection almost completely during the period of administration and for three weeks after the drug had been stopped. At three and four months after infection, however, bacilli were again detectable in the spleens of about half of the animals which had received isoniazid, and in a smaller proportion of the lungs. The conditions of this preliminary experiment differed, however, from the definitive experiments to be described in that the animals were already receiving isoniazid at the time of infection, while in the definitive experiments isoniazid was started eight weeks after infection.

OBSERVATIONS

Three experiments of the general design described above were conducted, but they differed in detail.

Mycobacterium tuberculosis strain Vallée was used for both primary infection and superinfection. The inoculum used for primary infection was calculated as containing only 13 culturable units per mouse. The challenge inoculum at eight weeks contained 5,000 bacilli, and the

challenge at sixteen weeks contained 7,000 bacilli. In table 3 the results of this experiment are summarized, showing the spleen counts achieved three and six weeks after each challenge.

Examining the counts three weeks after each challenge, a time when the bacillary population in the spleen is known to be at its height, it was evident that the mice which had received a small primary inoculum eight weeks before challenge had developed considerable immunity. This was evident from the fact that the bacilli of the superinfection achieved a count of only about one-tenth of that in the previously uninfected animals (C/B × 100 = 10.2 per cent). Measuring the immunity achieved sixteen weeks after primary infection in the same way, it may be seen that the previously infected mice were still immune, and that the degree of immunity had neither increased nor decreased in the second

TABLE 3

SPLEEN COUNTS (× 10^3) AT VARIOUS TIMES AFTER CHALLENGE

		Time after Challenge When Bacilli Counted	
		3 Weeks	6 Weeks
First Part: Challenge 8 Weeks after Beginning of Experiment			
Group B	No primary infection	378.0	34.5
Group C	Primary infection at beginning of experiment	38.5	16.5
	C/B × 100	10.2%	
Second Part: Challenge 16 Weeks after Beginning of Experiment			
Group D	No primary infection	268.0	75.8
Group E	Primary infection at beginning of experiment	25.8	39.6
Group F	Primary infection at beginning of experiment; isoniazid given from eighth to fifteenth weeks	21.4	17.6
	E/D × 100	9.6%	
	F/D × 100	8.0%	

Each number is the mean count of bacilli from 8–10 spleens.

TABLE 4

SPLEEN COUNTS (× 10^3) AT VARIOUS TIMES AFTER CHALLENGE

		Time after Challenge When Bacilli Counted	
		3 Weeks	5 Weeks
First Part: Challenge 8 Weeks after Beginning of Experiment			
Group B	No primary infection	574	156
Group C	Primary infection at beginning of experiment	42	29
	C/B × 100	7.3%	
Second Part: Challenge 16 Weeks after Beginning of Experiment			
Group D	No primary infection	545	99
Group E	Primary infection at beginning of experiment	72	30
Group F	Primary infection at beginning of experiment; isoniazid given from eighth to fourteenth weeks	29	16
	E/D × 100	13.2%	
	F/D × 100	5.3%	

Each number is the mean count of bacilli from 8–10 spleens.

period of the two months (E/D × 100 = 9.6 per cent). Moreover, the animals which had received isoniazid from the eighth to the fifteenth weeks showed the same counts after challenge as those which did not (compare *F* with *E*). This demonstrates that isoniazid given in this way did not interfere with the animals' immunity tested after withdrawal of the drug. The counts measured six weeks after challenge showed the same trend but with smaller differences between the various groups, no doubt because at this stage immunity resulting from the challenge infection itself was beginning to operate and, thus, to diminish the differences between the groups.

Bacilli in the lungs were enumerated in exactly the same way as in the spleens, and the same trend of results was observed. The individual variability of the lung counts was, however, much greater than in the spleens, so that the

mean differences between the groups do not reach significant levels.

The control *group A*, designed to follow the progress of the small primary infection, gave interesting results. Although mice developed clear-cut immunity as a result of this minute inoculum, organisms were rarely detectable in the organs of these mice; the infection presumably had either died out or become latent. Of 20 spleens examined at various times after infection, 13 showed no growth, and small numbers of tubercle bacilli were found in the others (mean of 12×10^3 per spleen in those giving a positive culture). Only 2 of 20 lungs showed any growth of *M. tuberculosis*.[4]

In a second experiment, strain Vallée was again used for the primary infection, and a somewhat larger inoculum of 130 culturable units per mouse was employed. The challenge infections were strain H37Rv in a dose of 2.6×10^5 culturable units per mouse for the first challenge (at eight weeks), and 1.9×10^5 culturable units per mouse for the second challenge (at sixteen weeks). The pattern and timing of the experiment were the same as in the first experiment except that the isoniazid was discontinued in *group F* two weeks before the challenge dose was administered.

In table 4, the spleen counts three and five weeks after each challenge are presented, and the results were very similar to those presented in table 3. Again, immunity was established at eight weeks and was no greater at sixteen weeks; isoniazid given from eight to fourteen weeks did not impair the animals' subsequent immunity. The small differences between the counts in *groups C, E,* and *F* are insignificant. Again, the differences were most apparent in the counts three weeks after challenge, when the bacterial population in the spleen was at its height, and were less marked at five weeks.

In this experiment the initial inoculum was larger than in *experiment 1*, and significant counts were obtained in *group A*. After an initial rise at four weeks to a mean of 101×10^3 per spleen, the populations settled in subsequent months to a mean of 29×10^3 per spleen, which did not vary significantly from month to month. Lung counts in this group were very variable.

In the third experiment, strain Vallée was used both for primary infection and for the challenge doses. Primary infection was initiated by 64 culturable units per mouse; the first challenge consisted of 3.3×10^4 bacilli per mouse and the second challenge, 7.4×10^4 units per mouse. The initial challenge was once more given eight weeks after primary infection, but this experiment differed from *experiment 1* in that there was a larger interval between the two challenges and a longer period of isoniazid treatment. The second challenge was given twenty-four weeks after the beginning of the experiment, that is, sixteen weeks after the initial challenge. The isoniazid group received the drug for the first fourteen of these sixteen weeks.

The results found in *experiments 1* and *2* were again found in the more prolonged experiment, as is shown in table 5. Again, animals receiving a small primary infection showed immunity at eight weeks; a similar degree of immunity was demonstrated four months later and was unaffected by the administration of isoniazid in the

TABLE 5

SPLEEN COUNTS ($\times 10^3$) AFTER CHALLENGE. MEAN OF COUNTS 20 AND 30 DAYS AFTER CHALLENGE

First Part: Challenge 8 Weeks after Beginning of Experiment		
Group B	No primary infection	69
Group C	Primary infection at beginning of experiment	14
	C/B × 100	20.3%
Second Part: Challenge 24 Weeks after Beginning of Experiment		
Group D	No primary infection	106
Group E	Primary infection at beginning of experiment	14
Group F	Primary infection at beginning of experiment; isoniazid administered from eighth to twenty-second weeks	30
	E/D × 100	13.2%
	F/D × 100	28.3%

Each number is the mean count of bacilli from 8–10 spleens.

[4] The methods of culture were the standard ones described earlier in the paper, and not the more sensitive techniques employed by McCune, Tompsett, and McDermott (J Exp Med, 1956, *104*, 763) in their studies of latent tuberculous infection in mice.

period after immunity had first become established.

The initial inoculum in this experiment was intermediate in size between those of the first two experiments, and the counts in *group A* were also intermediate in magnitude between those found in the preceding experiments. In this more prolonged test, mice of *group A* were examined at eight, sixteen, twenty-four, and twenty-eight weeks after infection. No microbial growth was obtained from 9 of 22 spleens. The mean count per spleen in the others was 9×10^3, and did not change appreciably from month to month. The lung counts of tubercle bacilli were again very variable.

Isoniazid susceptibility: Isoniazid susceptibility tests were done on a number of cultures from the spleen homogenates of *group F* in *experiments 1* and *3*, from mice which had received isoniazid for seven and fourteen weeks, respectively, starting eight weeks after infection. Twelve cultures from *experiment 1* tested in this way were all susceptible to less than 0.125γ per ml., as were 10 cultures from *experiment 3*. In addition, 12 cultures from a trial experiment (not described in this paper) were tested; this group had received isoniazid for eight weeks, starting eight weeks after infection, and the spleens were examined six weeks after isoniazid treatment was stopped. These cultures were also susceptible to less than 0.125γ per ml.

Discussion

The prevention of tuberculosis by isoniazid has been studied in a variety of experimental models during the last few years. In these experiments isoniazid has been administered before, at the same time as, or shortly after the bacterial inoculum, and a controversy soon arose about the effect of this sort of procedure on antituberculous immunity. It eventually became clear, mainly as a result of the work of Dubos and Schaefer (8), that, if infection was initiated with a small inoculum comparable to the dose likely in human infection, administration of isoniazid starting at about the time of infection did indeed suppress the animals' subsequent immunity. A large inoculum, on the other hand, provided an antigenic stimulus powerful enough to induce some immunity despite the effect of isoniazid in inhibiting its further multiplication. Inhibition of immunity by isoniazid was also shown by Schmidt (9) in monkeys which became naturally infected with tuberculosis while receiving isoniazid.

These experiments have a limited relevance to the problem in man because it is unusual to consider chemoprophylaxis in the uninfected subject. Most of the possible indications for chemoprophylaxis in man apply to people who have been infected long enough to have positive tuberculin reactions, and who probably already possess some degree of antituberculous immunity. Previous animal experiments have thus failed to reproduce accurately enough the conditions under which chemoprophylaxis is likely to be applied in man, both in this respect and in others discussed elsewhere (2). In the experiments described here, isoniazid has been administered to mice starting eight weeks after infection, at a time when immunity is already established. The main questions studied were whether the degree of immunity changed from this time onward and whether isoniazid, given in the way described, interfered with the animals' subsequent immunity.

The experiments agree in showing that: (*a*) eight weeks after primary infection, a substantial degree of antituberculous immunity is established; (*b*) immunity is still well defined sixteen and twenty-four weeks after infection and is of about the same degree as at eight weeks; and (*c*) the administration of isoniazid for various periods from eight weeks after infection has no adverse effect on the animals' immunity to subsequent challenge.

The experiments were designed to imitate as closely as possible the conditions under which isoniazid prophylaxis is most likely to be used in man. To what extent do they succeed in this aim? A small or very small inoculum was chosen for the primary infections since infection in man is probably initiated by a small number of bacilli. (Dubos and Schaefer (8) had shown that primary infection with a small number of virulent bacilli could induce an appreciable degree of antituberculous immunity in mice.) Mice which receive these small inocula remain perfectly healthy month after month, harboring a population of more-or-less quiescent bacilli; such animals may perhaps be compared with a healthy tuberculin-positive man who may also harbor quiescent bacilli for long periods of time. The time chosen for the first measurement of

immunity and for the beginning of isoniazid treatment in the mice was eight weeks after infection. By this time, in man, the infected subject has a positive tuberculin reaction and might be a subject for chemoprophylaxis with isoniazid. Furthermore, the actual technique of measuring immunity by counting organ populations of tubercle bacilli in large numbers of mice allows modest differences in immunity to be measured, differences of an order which might have some significance in determining whether a person develops tuberculous disease.

In certain respects, on the other hand, the experiments are a poor image of the conditions of human infection. First, and obviously, because they are done on mice and not on men. More particularly, in one important detail these experiments fail to reproduce the conditions of human infection. The animals received an inoculum widely and immediately spread through the body by intravenous injection, but the human sequence of primary complex formation is not reproduced in the experimental system. This difference might well be associated with differences in the rate of development of immunity and, perhaps, with other differences in the course of the infection.

On balance, it is possible to claim that these experiments have at least some relevance to the problem of chemoprophylaxis in man but, before the findings can be accepted, some possible defects of the experiments must be mentioned. The organ microbial counts in animals which had received a primary infection included the bacilli resulting from this infection as well as those resulting from multiplication of the challenge dose. The counts in these groups were therefore inaccurate in being greater than the true count resulting from the challenge infection alone. This error, however, tends to lessen the difference between the immunized and the nonimmunized groups, since it is in the animals immunized by the small primary inoculum that bacterial multiplication is limited. The differences which have been shown are therefore probably even greater than they appear to be in the tables. In each experiment, *group A* consisted of animals which had received the primary infection but no further challenge. Four mice from this group were killed at intervals, and the counts in *experiments 2* and *3* showed that, while initial multiplication of the small inoculum undoubtedly occurred, it was limited in degree. In *experiment 1* the initial inoculum was only 13 viable units, and organisms could not subsequently be cultured from most of the animals in *group A*; it is likely, however, that some multiplication of this minute inoculum did take place and was responsible for the immunity detectable in the infected mice. The magnitude of the error resulting from combined counting of the bacilli of primary infection with those of the challenge infection therefore, may not, be large. Several attempts were made to distinguish the bacilli of primary infection from those of the superinfection and thus to eliminate this source of error, but none was successful enough in giving reliable counts, and these experiments had to be discarded.

The same criticism is applicable to the drug-susceptibility tests, which were carried out on the tubercle bacilli from the spleens of experimental *group F*. These cultures were, of course, composed partly of bacilli from the challenge infection which, never having been exposed to isoniazid, would not be expected to be resistant to it. Not enough mice were available to leave part of *group F* unchallenged for drug-susceptibility tests only. The procedure was thought justifiable, since even a small number of resistant bacilli can be expected to grow out on subculture in the presence of isoniazid. The susceptibility tests are limited in number but do show that in the conditions of these experiments the administration of isoniazid is not followed by the emergence of resistant strains. These results are not likely to be easily applicable to man, partly because the duration of isoniazid is necessarily much shorter in experimental animals than in man, and partly because the host-parasite relationship in the experiments is much more uniform than it is likely to be in man. A tuberculin-positive patient without clinical or roentgenographic disease may yet harbor lesions of very variable extent and severity, and these variations will no doubt determine the chances of drug resistance. The drug-susceptibility tests only confirm what was already clear, that bacilli in a quiescent phase are not much affected by isoniazid and are unlikely to become resistant to it.

Summary

Antituberculous immunity was measured in mice at various times after a small primary

infection by determining the degree to which a larger challenge infection was able to multiply in the spleens and lungs of infected animals. Immunity was well established eight weeks after infection and did not subsequently increase, being present in the same degree sixteen and twenty-four weeks after infection.

Administration of isoniazid for various periods starting eight weeks after primary infection had no adverse effect on the animals' subsequent immunity.

The two main findings fit together well since, immunity having reached a plateau soon after infection, isoniazid would be unlikely to interfere with it and did not, in fact, do so. Tubercle bacilli isolated from the spleens of mice which had received isoniazid in the way described were all fully susceptible to the drug.

Sumario

El Influjo de la Quimioprofilaxis sobre la Inmunidad en la Tuberculosis Experimental

Se midió la inmunidad antituberculosa en ratones en varias ocasiones después de una pequeña infección primaria, determinando a qué proporción podía multiplicarse la infección en los bazos y pulmones de los animales infectados. La inmunidad estaba bien establecida a las ocho semanas de la infección y no aumentó después, revelando la misma intensidad a las dieciséis y las veinticuatro semanas de la infección.

La administración de isoniacida durante varios períodos de tiempo, comenzando a las ocho semanas de la infección primaria, mo ejerció efecto adverso sobre la subsiguiente inmunidad de los animales.

Los dos hallazgos principales se compaginan bien, dado que, habiendo alcanzado la inmunidad una meseta poco después de la infección, sería improbable que la isoniacida la obstacularizara, y, en efecto, no lo hizo. Los bacilos aislados de los bazos de los ratones que habían recibido isoniacida en la forma descrita fueron todos plenamente susceptibles a la droga.

Resume

L'influence de la chimioprophylaxie sur l'immunité dans la tuberculose expérimentale

L'immunité antituberculeuse fut mesurée chez des souris et à des époques différentes après une légère primoinfection, en déterminant le degré de multiplication possible dans les rates et les poumons des animaux infectés, en réponse à une sommation infectieuse plus importante. L'immunité fut bien établie huit semaines après l'infection et n'augmenta pas par la suite, étant présente au même degré seize et vingt quatre semaines après l'infection.

L'administration d'isoniazide pendant différentes périodes commençant huit semaines après la primoinfection n'eut pas d'effet contraire sur l'immunité ultérieure de l'animal.

Les deux principales données vont bien ensemble, puisque, l'immunité ayant atteint son plateau aussitôt après l'infection, l'isoniazide serait vraisemblablement incapable de la gêner et ne le fit pas en fait. Des bacilles isolés à partir des rates de souris qui ont reçu de l'isoniazide de la façon décrite ci-dessus furent tous entièrement sensibles au médicament.

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REFERENCES

(1) Mitchison, D. A.: Prophylactic chemotherapy, in *Advances in Tuberculosis Research*, Vol. VIII, H. Birkhauser and H. Bloch, ed., S. Karger, AG, Basel, 1957.

(2) Lambert, H. P.: The chemoprophylaxis of tuberculosis: A review, Amer Rev Resp Dis, 1959, *80*, 648.

(3) International Symposium of the Deborah Sanatorium and Hospital, Amer Rev Resp Dis, 1959, *80* (Supplement, October, p. 1).

(4) Ferebee, S. H., Mount, F. W., and Anastasiades, A. A.: Prophylactic effects of isoniazid on primary tuberculosis in children: A preliminary report, Amer Rev Tuberc, 1957, *76*, 942.

(5) Fenner, F., Martin, S. P., and Pierce, C. H.: The enumeration of viable tubercle bacilli in cultures and infected tissues, Ann NY Acad Sci, 1949, *52*, 751.

(6) McCune, R. M., and Tompsett, R.: Fate of *Mycobacterium tuberculosis* in mouse tissues as determined by the microbial enumeration technique, J Exp Med, 1956, *104*, 737.

(7) McCune, R. M., Deuschle, K., and McDermott, W.: The delayed appearance of isoniazid antagonism by pyridoxine *in vivo*, Amer Rev Tuberc, 1957, *76*, 1100.

(8) Dubos, R. J., and Schaefer, W. B.: Antituberculous immunity induced in mice by virulent primary infection: Its inhibition by chemoprophylaxis, Amer Rev Tuberc, 1956, *74*, 541.

(9) Schmidt, L. H.: Some observations on the utility of simian pulmonary tuberculosis in defining the therapeutic potentialities of isoniazid, Amer Rev Tuberc, 1956, *74* (Supplement, p. 138).

RETENTION OF AEROSOL PARTICLES IN THE RESPIRATORY TRACT[1]

A Review

R. I. MITCHELL

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Introduction

The purpose of this paper is to review the existing literature dealing with the retention of particulate matter in the respiratory tract, with special emphasis on the effect of particle size. Because of the importance of inhaled dust particles as industrial hazards, exhaustive study has been done of their injurious effects. Many investigations of pneumoconiosis associated with the mining industry were carried out during the first quarter of the twentieth century. Since that time, the literature on this subject has become so extensive that much time and space would be required to review all papers dealing with lung retention. Those papers on pneumoconiosis that are concerned only with dust loading, and not with the particle-size distribution of the dust, have not been included in the present review, in which the emphasis is on the effects of particle size.

During the past few years, interest in aerosol therapy, chemical warfare, and the dangers associated with radioactivity has resulted in numerous papers dealing with the action of inhaled particles. Most of these papers appear to have considerable merit; however, because of differences in the techniques used to determine the retention of the particles as a function of particle size, agreement on the results presented by various investigators is poor. An attempt has been made, however, to evaluate the reliability that can be placed on the data obtained by the various techniques.

Mechanisms of Deposition

The mechanisms involved in the deposition of inhaled particles are related to the physical and chemical properties of the dust as well as to the anatomy and physiology of the respiratory tract. Both theoretic and experimental considerations have shown that particles are deposited in the respiratory tract by one of the following three mechanisms:

Inertial impaction: A particle suspended in an air stream is not able to follow the stream because of its inertia as it moves through the passages of the respiratory tract and is deposited against the walls of the passage. Inertial impaction is an important mechanism in the nasal airways and in the upper lung, where the air velocity is fairly high. Landahl and Herrmann (1), May (2), and Rosin and co-workers (3) have studied the deposition of particles in curved tubes and have shown that the larger particles are likely to be separated by this mechanism. The inertial effect on the particles is directly proportional to the density and to the square of the particle diameter.

Sedimentation: Because of gravitational effects, a particle will settle downward. This mechanism is one of the more important causes of deposition of larger particles in the deeper portion of the lungs, where the air velocity has been reduced. The sedimentation rate is proportional to the density and to the square of the particle diameter; therefore, the more massive particles that have survived the inertial influence in the upper respiratory tract will be deposited by sedimentation. The settling rate for small particles can be calculated from Stokes' law.

Brownian motion: In the alveolar sacs, in which the air velocity is quite low, Brownian motion becomes an important mechanism in the removal of particulate matter. Very small particles suspended in air are in continuous motion because of being bombarded by air molecules. The mean displacement after a given time can be computed from Einstein's (4) diffusion equation. From this equation, it is then possible to calculate the rate of removal of particles by diffusion.

Findeisen (5), in his theoretic study of retention, applied all three of the above mechanisms to determine retention of particles in the bronchial tree.

Methods of Producing Aerosols for Experimental Studies

The most common method of producing an aerosol for retention studies is by dispersion of dusts or atomization of test liquids, as was done by Morrow and co-workers (6), Landahl and

[1] From the Battelle Memorial Institute, Columbus 1, Ohio.

Black (7), Dautrebande and co-workers (8, 9), Palm and associates (10), and others. The particle-size distribution of the aerosols produced by this method of generation is very broad, and it is difficult to interpret the retention data. For most of these experiments, the retention is plotted as a function of the number or mass median diameter. Brown (11) also produced dust aerosols by dispersing preclassified solid materials suspended in a water solution by means of a nebulizer. The droplets containing the particulate matter were dried before sampling.

The studies most applicable to this survey on retention in the respiratory tract are those made by Altshuler and co-workers (12), Wilson and LaMer (13), and Landahl and co-workers (14, 15), using monodispersed aerosols. The monodispersed aerosols were produced by the careful control of condensation of the test liquid on condensation nuclei. The advantages of using homogeneous or monidispersed aerosols are that the particles are nearly uniform in size and their diameter is, therefore, easily measured. When a polydispersed aerosol is inhaled, the distribution of sizes obscures the relationship between particle size and retention.

Buckland and co-workers (16) also produced monodispersed aerosols by the atomization of slurries of *Bacillus subtilus* spores tagged with radioactive phosphorus. After the liquid evaporated, the aerosol was composed of spores of uniform size about 1 μ in diameter. Goldberg and Leif (17) produced aerosols of *Pasteurella pestis* bacteria which had been tagged with radioactive phosphorus. The diameter of the aerosol particles formed was also 1 μ.

Theoretical Studies of Retention in Man

Mathematical models have been used by Findeisen (5), Wilson (18), Hatch and Hemeon (19), Trurnit (20), Davies (21), Landahl (22), Berghaus (23), and Eisenbud (24) to estimate the amount of retention for particulate matter of various sizes in the respiratory tract.

The first classical treatment of theoretic retention was made by Findeisen in which he computed the average dimensions of the adult tracheobronchial tree according to a functional concept of structure rather than a strictly anatomic description. For this study, the following assumptions were also made:

(*1*) The breathing passages were assumed to be straight tubes the length, width, and position of which were approximately in accordance with anatomic data. The alveolar sacs were assumed to be hollow spheres.

(*2*) Inhalation and exhalation were assumed to take place at equal and constant rates of 200 cc. per second for a time cycle of

TABLE 1

Landahl's Schematic Representation of Respiratory Tract

Region	Number	Volume	Relative Volume	Diameter	Length	Cross-section Area	Velocity	Passage Time (A)	Fration Passing (B)	(A × B)
		cc.		*cm.*	*cm.*	*cm²*	*cm./sec.*	*sec*		
Mouth	1	20	0.04	2	7	3	100	0.07	1.00	0.07
Pharynx	1	20	0.04	3	3	7	45*	0.07	0.96	0.06
Trachea	1	25	0.06	1.6	12	2	150	0.08	0.92	0.074
Primary bronchi	2	10	0.02	1.0	6	0.8	190	0.032	0.86	0.027
Secondary bronchi	12	4	0.01	0.4	3	0.12	210	0.014	0.84	0.012
Tertiary bronchi	100	5	0.01	0.2	1.5	0.03	100	0.015	0.83	0.012
Quaternary bronchi	770	7	0.015	0.15	0.5	0.018	22	0.023	0.82	0.02
Terminal bronchioles	6×10^4	50	0.11	0.06	0.3	2.8×10^{-3}	1.8	0.17	0.81	0.14
Respiratory bronchioles	1.5×10^5	30	0.06	0.04	0.15	1.2×10^{-3}	1.7	0.09	0.70	0.06
Alveolar ducts I	3×10^6	100	0.22	0.03	0.05	7×10^{-4}	0.14	0.36	0.64	0.25
Alveolar ducts II	4×10^7	600	0.42	0.025	0.03	4.9×10^{-4}	0.015	2.0	0.42	0.83
Alveolar sacs	10^8	2000	0	0.033	0.033		0			

* Glottis velocity = 150

TABLE 2

PER CENT RETENTION IN VARIOUS REGIONS OF THE RESPIRATORY TRACT AS CALCULATED BY LANDAHL

Region	300 cc/sec, 4-sec cycle, 450 cc Tidal Air					300 cc/sec, 8-sec Cycle, 900 cc Tidal Air					300 cc/sec, 12-sec Cycle, 1,350 cc Tidal Air					1,000 cc/sec, 4-sec Cycle, 1,500 cc Tidal Air				
	Particle Diam, μ					Particle Diam, μ					Particle Diam, μ					Particle Diam, μ				
	20	6	2	0.6	0.2	20	6	2	0.6	0.2	20	6	2	0.6	0.2	20	6	2	0.6	0.2
Mouth	15	0	0	0	0	14	1	0	0	0	14	1	0	0	0	18	1	0	0	0
Pharynx	8	0	0	0	0	8	1	0	0	0	8	1	0	0	0	10	1	0	0	0
Trachea	10	1	0	0	0	11	1	0	0	0	11	1	0	0	0	19	3	0	0	0
Primary bronchi	12	2	0	0	0	13	2	0	0	0	13	1	0	0	0	20	5	0	0	0
Secondary bronchi	19	4	0	0	0	17	4	1	0	0	18	5	1	0	0	21	12	3	0	0
Tertiary bronchi	17	9	0	0	0	20	9	1	0	0	21	10	1	0	0	9	20	4	1	0
Quaternary bronchi	6	7	1	0	0	8	7	1	0	0	8	7	1	0	1	1	10	2	0	0
Terminal bronchioles	6	19	4	2	2	6	24	6	2	2	6	24	6	1	2	1	9	2	0	0
Respiratory bronchioles	0	11	4	2	2	0	10	4	2	2	0	12	4	2	2	0	3	1	2	2
Alveolar ducts I	0	25	16	5	6	0	27	19	7	9	0	27	20	8	8	0	13	10	4	5
Alveolar ducts II	0	5	28	10	9	0	5	48	21	18	0	5	49	24	23	0	17	41	16	14
Alveolar sacs	0	5	0	0	0	0	0	0	0	0	0	0	5	8	7	0	1	7	5	7
Total	93	83	51	19	19	97	91	80	32	31	99	94	87	43	43	98	95	70	28	28

2 seconds without any pause between inhaling and exhaling.

(3) Sedimentation and diffusion mechanisms of deposition in the breathing passages were considered, as well as initial deposition at branching points of the passages. Deposition during both inhaling and exhaling was taken into account.

For the retention calculations, the particle radius was varied from 0.3 to 30 μ. Also, in order to simplify the calculations, Findeisen assumed that the flow velocities were equal over the entire tube cross section. This assumption would increase slightly the deposition values for each region of the respiratory tract.

Landahl (22) modified Findeisen's calculations, using slightly different dimensions of the tracheobronchial tree, and computed retention values for several flow rates. The schematic representation of the respiratory tract used by Landahl is shown in table 1.

The theoretic retention results obtained for four different breathing patterns and for five different particle sizes are summarized in table 2.

Figure 1 is a schematic representation of the anatomy of the pulmonary tree showing the results of Landahl. This illustration indicates that particles 20 μ and larger are removed completely before they leave the terminal bronchioles. The majority of the particles 6 μ in diameter are removed before they reach the lower alveolar ducts, and almost all of the particles of 2.0 μ size and greater are removed in the lower alveolar ducts. Landahl's calculations show substantially no removal of particles of any size by the alveolar sacs, whereas Findeisen showed as much as 45 per cent removal of 2.0 μ particles.

EXPERIMENTAL STUDIES OF RETENTION IN MAN

The amount of material that deposits in the respiratory system and the depth to which it penetrates before deposition are functions of particle size. Therefore, considerable attention has been given to determining exactly how the two variables are related. Experiments were conducted with naturally occurring dusts and with homogeneous or heterogeneous aerosols produced in the laboratory.

Retention of Naturally Occurring Dusts

Disease has been attributed to dusts since ancient times. One of the first references to disease caused by dust and fumes appears in the writing in the first century A.D. by Plenius (25) who described the devices used by ore refiners to prevent the breathing of "fatal dusts."

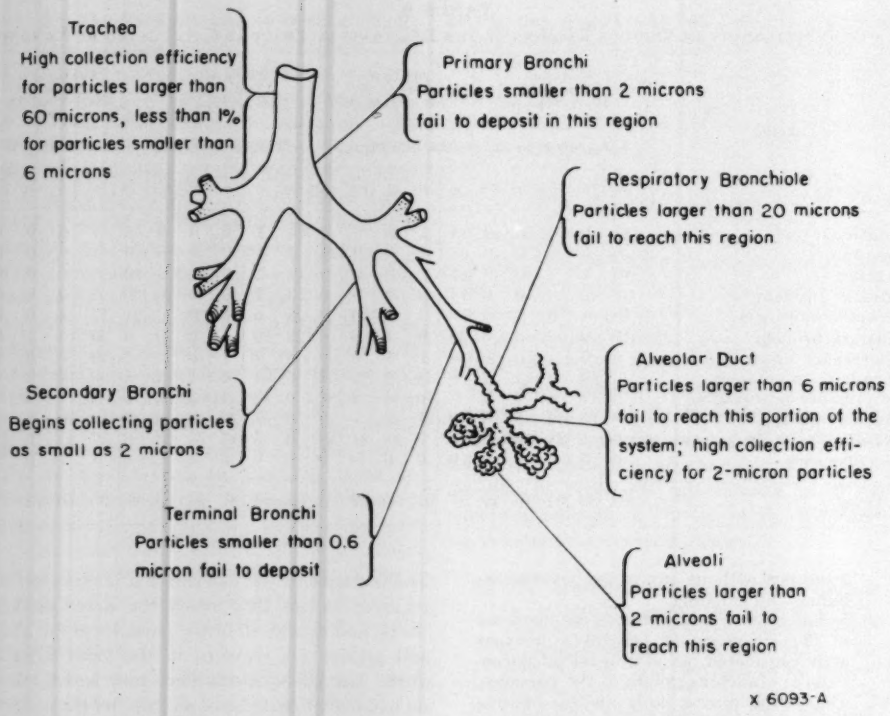
Trachea
High collection efficiency for particles larger than 60 microns, less than 1% for particles smaller than 6 microns
Primary Bronchi
Particles smaller than 2 microns fail to deposit in this region
Respiratory Bronchiole
Particles larger than 20 microns fail to reach this region
Alveolar Duct
Particles larger than 6 microns fail to reach this portion of the system; high collection efficiency for 2-micron particles
Secondary Bronchi
Begins collecting particles as small as 2 microns
Terminal Bronchi
Particles smaller than 0.6 micron fail to deposit
Alveoli
Particles larger than 2 microns fail to reach this region
x 6093-A

FIG. 1. Schematic representation of the anatomy of the pulmonary tree showing theoretic retention computed by Landahl.

The majority of the information on retention of naturally occurring dusts in the lungs arises from histologic studies. Information on chronic exposure can be found in studies by Gessner and co-workers (26), Bedford and Warner (27), Brown (11), Thomas and Stegemann (28), Moir (29), and McCrae (30). By comparing the size distribution of dust found in the lungs with that found in the exposure site, a rough estimate can be made of the retention of insoluble particles. This technique is seriously affected by the ciliary cleansing action of the bronchial tree.

The studies by Van Wijk and Patterson (31) were carried out in a gold mine where natural dusts of quartzite were being generated.

They used two thermal precipitators to collect a sample before and after inhalation. For these experiments, the test subject breathed through the apparatus for about ten minutes to allow his lungs to come to equilibrium with the dusty air. The inhaled and exhaled samples were then collected for a period of about twenty minutes. The particle-size distribution of the collected particles was then determined with a microscope fitted with a specially calibrated graticule.

Their results failed to show a minimum of retention in the 0.4 μ range; however, the high percentage of retention for the larger sizes was in good agreement with the theoretic predictions.

Retention of Heterogeneous Experimental Aerosols

Many data on the retention of aerosols in the respiratory tract have been obtained with heterogeneous aerosols because they are so easily generated. Most of these aerosols were produced by the direct atomization of dry powders, solutions, slurries, or pure liquids. The particle-size

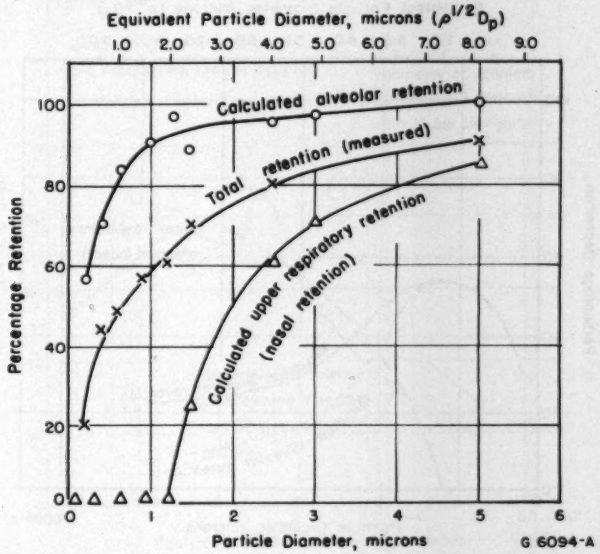

FIG. 2. Lung retention of clay dusts as a function of particle size (32).

distribution of this type of aerosol is quite broad, and much of the meaning becomes obscure when an "average" diameter is used to represent the size distribution of the aerosol. Important studies using heterogeneous aerosols have been reported by Brown and co-workers (32), Landahl and co-workers (7, 1), Lehmann and co-workers (33), Lehmann (34), Milburn and co-workers (35), Worth and Schiller (36), Dautrebande and co-workers (8, 9, 37), Drinker and co-workers (38), Davies (21), and Morrow and co-workers (6), Baumberger (39), and Sayers and co-workers (40).

In the studies by Dautrebande and co-workers (9), the aerosol was partially classified by passing it through scrubbers before inhalation to remove the larger particles. The particulates used by Brown and co-workers (32) were classified into very narrow bands before dissemination to produce aerosols.

Dautrebande and co-workers (41) also studied the retention of submicronic dusts with number mean diameter which varied from 0.1 μ to 0.8 μ.

Figure 2 is a summary of 100 tests by Brown, using nasal inhalation techniques for clay dust particles having number median diameters from 0.24 to more than 5 μ. This figure shows that upper respiratory retention is about 85 per cent for particles 5 μ in diameter and drops off to zero for particles about 1 μ in diameter The curve for measured retention is very similar to that obtained by Van Wijk and Patterson (31). The curve for alveolar retention shows that more than 90 per cent of the 1 to 5 μ particles which pass the upper respiratory tract are retained in the alveolar region.

Figure 3 is a plot of the percentage retention of inhaled dust in the upper respiratory tract and alveoli in relation to particle size. The data for this curve were calculated from the data in figure 2. The main conclusion drawn from these curves is that the optimal equivalent particle size for maximal alveolar retention is approximately 2 μ.

Brown's experimental size range did not include particles smaller than about 0.25 μ. If the density factor is considered, the smallest equivalent particle diameter becomes about 0.4 μ, which is essentially the critical size for minimal retention obtained by other investigators.

Morrow and co-workers (6) determined the retention of submicronic aerosols of sodium

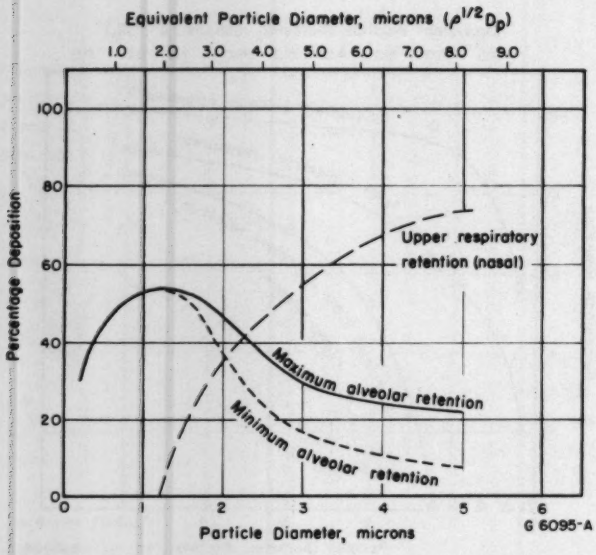

FIG. 3. Theoretic deposition of clay dusts in the upper respiratory tract and alveoli (32).

chloride. The particles had a number median diameter of 0.052 μ and a geometric standard deviation of 2.26. The results of these experiments indicate 63 per cent retention. No attempts were made to determine how hygroscopicity may cause the particle diameter to change after inhalation into the lungs, in which the humidity is nearly 100 per cent.

In the studies of Landahl and Herrmann (1) and others who used cascade impactors for sampling aerosols before and after inhalation, the retention was based on the classified fractions in the device. Thus, the particle-size distribution for each fraction was fairly narrow. However, the distribution was still broad enough to obscure any abrupt change in the relationship between particle size and retention. This difficulty can be eliminated by the use of monodispersed aerosols.

Retention of Monodispersed Aerosols

Monodispersed aerosols are aerosols in which all of the particles are of the same size. It is possible to produce nearly monodispersed aerosols by the atomization of extremely dilute slurries of carefully prepared polystyrene beads of uniform size and of certain species of bacteria and spores. Mists of a high degree of uniformity can also be produced by a LaMer type (42) of generator. The most accurate data concerning respiratory retention have been obtained by Wilson and LaMer (13), Altshuler and co-workers (12), and Landahl and co-workers (14, 15), using monodispersed aerosols produced in a LaMer generator.

Wilson and LaMer produced glycerol aerosols on condensation nuclei of radioactive sodium chloride.

The droplets were then diluted to 50 per cent glycerol by volume by passing the aerosol through a conditioning chamber containing an equivolume glycerol-water solution. After the aerosol had come to equilibrium, the output rate was measured by collecting a sample on a filter. The test subject was then allowed to inspire the aerosol by a mouthpiece, and the amount of material exhaled was collected on a filter. After correcting for losses in the tubing, it was then possible to calculate the retention rate for various particle sizes.

For these tests, no correction was made for the growth of the aerosol particles by absorption of water vapor from the saturated air in the lungs. Because of the highly hygroscopic nature of this type of aerosol, it will continue to grow as long as it is in contact with the humid atmosphere of the lungs. By assuming that the aerosol comes to equilibrium at only 97 per cent humidity within

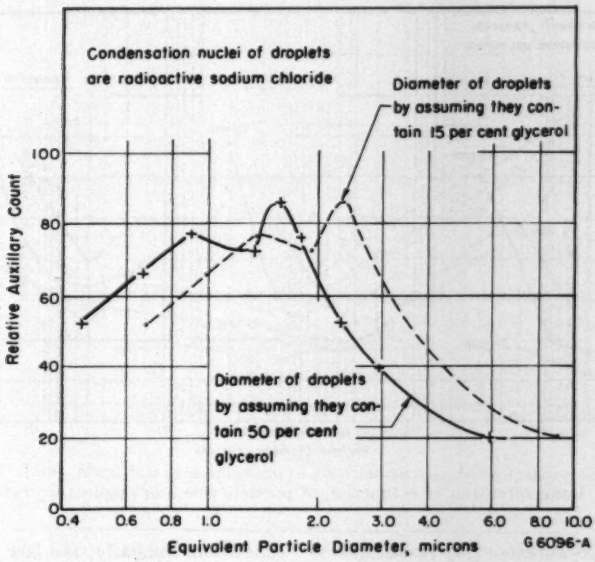

FIG. 4. Average relative auxiliary radioactive counts as a function of equivalent particle diameter obtained by Wilson and LaMer.

the lungs, the particles will increase in diameter by 53 per cent, which appears to be a more realistic increase than the 20 per cent predicted by the experimenters.

In addition to measuring the total retention directly, an estimate of the amount of alveolar retention was made by placing a Geiger-Mueller counter against the chests of the test subjects. The radiation intensity detected by the counter is a close approximation to the quantity of aerosol retained in the finer respiratory passages.

Figure 4 is a plot of the average relative auxiliary radiation counts, recorded in the chest region under the armpits as a function of particle diameter. In this figure it may be seen that the most effective size range for retention in the alveoli is between 0.6 and 2.4 μ in diameter. The curve also has a double peak which suggests that the upper respiratory tract exerts a maximal filtering efficiency at some particular size producing a minimum of alveolar retention for that size.

In the studies by Altshuler and co-workers (12), monodispersed aerosols of triphenyl phosphate were used. Triphenyl phosphate was chosen as the test material because it met the requirements of the generator, is not very toxic, and is nonhygroscopic. The size of the particles used was varied from 0.14 to 3.2 μ covering the region of minimal retention. The particle-size measurements were made with the microscope, by determining terminal velocity for free fall, and with the tyndallometer.

Figure 5 is a summary of the deposition data obtained for three different test subjects and three different respiratory rates. A definite minimum of retention in the neighborhood of 0.4 μ, which was predicted by Findeisen is shown in this figure, as well as a greater retention for slow deep breathing than for shallow fast breathing. The effect of breathing rate is much more pronounced for the large 1.6 μ particles than for the small 0.14 μ particles. For the larger 1.6 μ particles, the mechanism of removal is impaction and sedimentation, the latter being a function of the first power of residence time. For the smaller particles, the mechanism of removal is Brownian motion which produces an exponential decay and is approximately related to the square root of residence time after a loss of a high percentage of the particles.

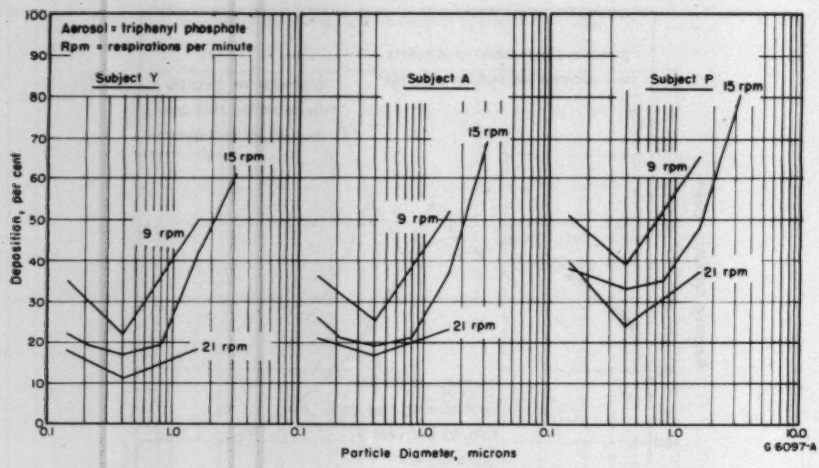

FIG. 5. Lung retention as a function of particle size and respiratory rate (12).

Landahl and co-workers (14) used monodispersed aerosols of tricresyl phosphate in their retention studies. The range of equivalent particle diameters, corrected to unit density, varied from 0.11 to 6.3 μ. The results of their tests also show a definite minimum of retention in the 0.5 μ range.

In these studies, an effort was made to determine the variability of retention of the aerosol particles by different subjects. A total of 21 male and 3 female subjects participated. The diameter of the uniformly sized droplets was 0.25 μ. The breathing cycle was 12 seconds and the tidal volume was 1,350 cc. at a rate of 300 cc. per second. The average retention was 41 per cent, with a standard deviation of 5.1 per cent.

In addition to determining the retention as a function of particle size, Landahl and co-workers also studied the effect of respiration pattern and residence time on retention.

Retention for Various Patterns of Respiration and Residence Time

An important variable in the retention of particulate matter in the respiratory tree is the length of time the particles remain in the system. Those particles which are first to enter the respiratory tract are the last to leave during exhalation. Similarly, the last particles to enter the system are the first to leave. Landahl and co-workers have determined the fraction of particulates expired for five different breathing patterns. Three of the patterns were at a breathing rate of 18 liters per minute, which represents light work conditions, and the remainder were at a rate of 60 liters per minute, which represents extra heavy work conditions.

Figure 6 summarizes the results obtained at a breathing rate of 18 liters per minute. That there is little loss of the smaller particles in the first fraction of expired air is shown in the figures. Similar results were obtained at a flow rate of 60 liters per minute. At the same respiratory pattern as the low flow rate, the retention was slightly higher.

EXPERIMENTAL STUDIES OF RETENTION IN ANIMALS

Animals have played an important role in medical research on lung retention because histologic studies can be made immediately after exposure. Also, the effects of materials on lung tissue which would be too dangerous for human inhalation can be studied. Some of the long list of papers that deal with inhalation studies in animals are those of Cauer and Neymann (43), Neymann (44), Beckman (45), Goldberg and

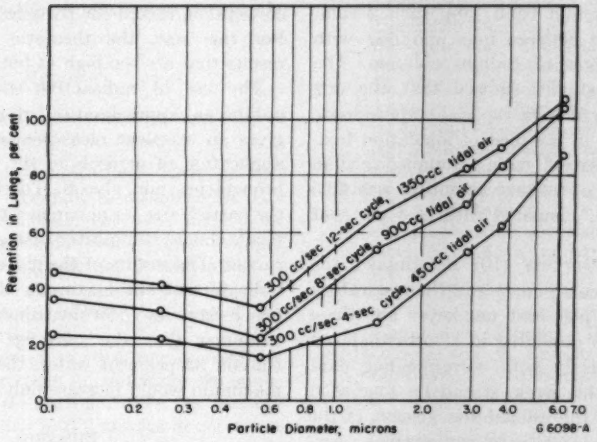
Retention in Lungs, per cent
300 cc/sec 2-sec cycle, 1350-cc tidal air
300 cc/sec 3-sec cycle, 900-cc tidal air
300 cc/sec 4-sec cycle, 450-cc tidal air
Particle Diameter, microns
G 6098-A

FIG. 6. Lung retention as a function of particle size and respiratory rate (14).

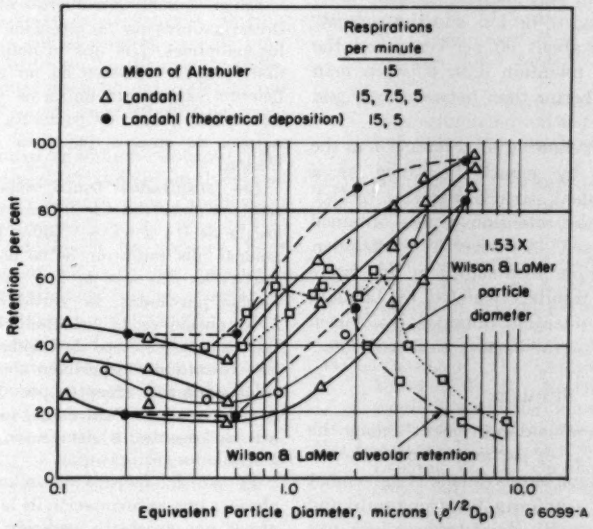
Respirations per minute
Mean of Altshuler 15
Landahl 15, 7.5, 5
Landahl (theoretical deposition) 15, 5
1.53 X Wilson & LaMer particle diameter
Wilson & LaMer alveolar retention
Retention, per cent
Equivalent Particle Diameter, microns
G 6099-A

FIG. 7. Comparison of lung retention data obtained by three different investigators.

Leif (17), Scott and co-workers (46, 47), Barrett and co-workers (48), Verzar and co-workers (49), Hatch and Kindsvatter (50), Shoshkes and co-workers (51), Asset and co-workers (52), Punte (53), Cohn and co-workers (54), Buckland and co-workers (16), Ishikawa and Drinker (55), Wilson and co-workers (56, 57), Morrow and Gibb (58), and Palm and co-workers (10).

To evaluate the results of animal inhalation studies as related to the retention in man, a direct comparison must be made between man and the animal using the same aerosol. In a recent

study by Morrow and Gibb (58), such a comparison was made between man and dog with submicronic aerosols of sodium chloride. The results of these studies showed that the dog should be considered to be especially appropriate for investigations in the filed of inhalation toxicology. For an aerosol with a number median diameter of 0.04 μ, average retention was 66.5 per cent for dogs, compared with 63.4 per cent for man.

Palm and co-workers (10) determined the retention of particulate matter in the respiratory tract for guinea pigs and monkeys. For these animals, data are presented in a form that can be compared directly with corresponding data for man. From this work, it can be concluded that the smaller the animal the greater is the over-all retention for a given particle size; alveolar efficiency of animals was not significantly different from that of man; the particle size for which data on man and animals compare most favorably was found to be 1 μ, and the percentage retention was about 50 per cent; and the agreement of the retention data between man and monkey was better than between man and guinea pig.

Figure 7 is a plot showing total retention in the respiratory tract by mouth breathing as a function of equivalent particle diameter ($\rho^{\frac{1}{2}}D_p$). This plot shows the retention results obtained with monodispersed aerosols by Altshuler, Landahl, and Wilson. Also shown in this figure are the theoretic results calculated by Landahl and the alveolar retention obtained by Wilson and LaMer based on radioactive measurements.

Summary

There is considerable disagreement among the various investigators of particle retention in the lungs. The two major causes of lack of agreement are failure to use a uniform breathing rate and the use of a mean particle size to describe a test aerosol which has a wide-size distribution.

Both the experimental and theoretic results show a minimum of retention in the 0.4 to 0.6 μ range. All of the data also indicate 90 per cent or more retention of particles greater than 7 μ. In addition to particle size, the next largest variable affecting retention is breathing rate. The theoretic calculations of Landahl agree well with the experimental results obtained by Landahl and co-workers, except for particles in the 2 μ range. For this size, the theoretic calculations give results that are too high at both breathing rates.

The use of radioactive sodium chloride to obtain an approximation of alveolar retention gives an excellent measurement for therapeutic application of aerosols in the smaller branches, bronchioles, and alveoli. To establish definitely the particle size for maximal retention, the experiments should be repeated, using a nonhygroscopic carrier. The results of the glycerol-water aerosols indicate that the maximum occurs for particles which have an equivalent diameter of 1.5 μ. By assuming that the particles grow until they contain 85 per cent water, the diameter for the maximum would increase only to 2.3 μ.

Sumario

El Depósito de Partículas de Aerosoles en el Aparato Respiratorio. Reseña

Existe mucho desacuerdo entre los distintos investigadores de la retención de partículas en los pulmones. Las dos principales causas de la discrepancia consisten en no emplearse un coeficiente respiratorio uniforme y en el empleo de un tamaño medio de partícula para describir un aerosol de ensayo que goza de amplia distribución.

Les resultados tanto experimentales como teóricos muestran un mínimo de retención en la escala de 0.4 a 0.6 γ. Todos los datos indican además una retención de 90 por ciento o más de partículas mayores de 7 γ. Además del tamaño de las partículas, la variable que afecta más la retención es la velocidad de la respiración. Los cálculos teóricos de Landahl concuerdan con los resultados experimentales de Landahl y colaboradores, excepto por las partículas de 2 γ de tamaño. Para éstas, los cálculos teóricos arrojan resultados demasiado altos con ambas velocidades respiratorias.

El uso del cloruro de sodio radioactivo para obtener una aproximación de la retención alveolar ofrece una excelente medición para la aplicación terapéutica de los aerosoles en las ramas más pequeñas, los bronquíolos y los alvéolos. Para establecer definitivamente el tamaño de las partículas que hallarán retención máxima, hay que repetir los experimentos, usando un portador anhigroscópico. Los resultados de los aerosoles de glicerina-agua indicaron que se obtiene el máximo con partículas que tienen un diámetro equivalente de 1.5 γ. Dando por sentado que las partículas crecen hasta que contienen 85 por ciento

de agua, el diámetro para el máximo no aumentaría más que a 2.3 γ.

Resume

Déposition de particules dans les voies respiratoires par aérosol. Une revue

Il y a beaucoup de mésentente entre les différents chercheurs étudiant la rétention de particules dans les poumons. Les deux principales causes de désaccord sont l'echec dans l'emploi d'une évaluation uniforme de la respiration et l'emploi d'une taille moyenne de particules pour décrire un examen au moyen d'un aérosol qui ait une large distribution.

Les résultats théoriques ainsi que les résultats expérimentaux montrent un minimum de rétention de l'ordre de 0,4 à 0,6 μ. Toutes les données indiquent aussi qu'il y a 90% ou plus de rétention de particules plus grandes que 7 μ. En plus de la taille des particules, le facteur variable qui affecte le plus la rétention est la vitesse de respiration. Les calculs théoriques de Landahl concordent bien avec les résultats expérimentaux obtenus par Landahl et ses collaborateurs, excepté pour les particules de l'ordre de 2 μ. Pour cette taille, les calculs théoriques donnent des résultats qui sont trop élevés dans les deux vitesses de respiration.

L'emploi de chlorure de sodium radioactif, pour obtenir approximativement la rétention alvéolaire, donne une excellente mesure pour l'application thérapeutique d'aérosols dans les plus petites bronches, les bronchioles et les alvéoles. Pour établir définitivement la taille des particules pour obtenir une rétention maxima, les expériences devraient être répétées en employant un transporteur non-hydroscopique. Les résultats avec des aérosols d'eau glycérinée indiquent que le maximum se produit pour des particules qui ont un diamètre équivalent à 1,5 μ. En présumant que les particules augmentent jusqú'à ce qu'elles contiennent 85% d'eau, le diamètre pour obtenir le maximum devrait augmenter seulement de 2,3 μ.

REFERENCES

(1) Landahl, H. D., and Herrmann, R. G.: On the retention of air-borne particulates in the human lung, J Industr Hyg, 1948, *30*, 181.

(2) May K. R.: The cascade impactor, J Sci Instr, 1945, *22*, 187.

(3) Rosin, P., Rammler, E., and Intelman, W.: Fundamentals and limitations of cyclone dusting, VDI Zeitschrift, 1932, *76*, 433.

(4) Einstein, A.: Uber die von der molecular-kinetishen Theorie der Warmer geforderte Bewegun von in rohenden Flüssigkeiton suspendierten Teilchen, Annulen der Physik, 1905, *17*, 549.

(5) Findeisen, W.: Uber das Absetzen kleiner, in der Luft suspendierter Teilchen in der menschlichen Lunge bei der Atmung, Pflueger Arch ges Physiol, 1935, *236*, 367.

(6) Morrow, P. E., Mehrhof, E., Casarett, L. J., and Morken, D. A.: An experimental study of aerosol deposition in human subjects, AMA Arch Industr Health, 1958, *18*, 292.

(7) Landahl, H. D., and Black, S.: Penetration of air-borne particulates through the human nose, J Industr Hyg, 1947, *29*, 269.

(8) Dautrebande, L., Beckman, H., and Walkenhorst, W.: Ritenzione polmonare delle particelle submicroniche e submicroscopiche, presented before 2a Giornata internazionale di Aerosologia, June 3, 1954.

(9) Dautrebande, L., Beckmann, H., and Walkenhorst, W.: Lung deposition of fine dust particles, AMA Arch Industr Health, 1957, *16*, 179.

(10) Palm, P. E., McNerney, J. M., and Hatch, T.: Respiratory dust retention in small animals, AMA Arch Industr Health, 1956, *13*, 355.

(11) Brown, C. E.: Quantitative measures of the inhalation retention and exhalation of dusts and fumes by man: II, J Industr Hyg, 1931, *13*, 285.

(12) Altshuler, B., Yarmus, L., Palmes, E. D., and Nelson, N.: Aerosol deposition in the human respiratory tract: I. Experimental procedures and total deposition, AMA Arch Industr Health, 1957, *15*, 293.

(13) Wilson, I. B., and LaMer, V. K.: The retention of aerosol particles in the human respiratory tract as a function of particle radius, J Industr Hyg, 1948, *30*, 265.

(14) Landahl, H. D., Tracewell, T. N., and Lassen, W. H.: Retention of air-borne particulates in the human lung: III, AMA Arch Industr Hyg, 1952, *6*, 508.

(15) Landahl, H. D., Tracewell, T. N., and Lassen, W. H.: On the retention of air-borne particulates in the human lung, II, AMA Arch Industr Hyg, 1951, *3*, 359.

(16) Buckland, F. E., Harper, G. J., and Morton, J. D.: Use of spores labelled with radiophosphorus in the study of the respiratory retention of aerosols, Nature (London), 1950, *166*, 354.

(17) Goldberg, L. J., and Leif, W. R.: The use of a radioactive isotope in determining the retention and initial distribution of air-borne bacteria in the mouse, Science, 1950, *112*, 299.

(18) Wilson, J. B.: The deposition of charged particles in tubes with reference to the

retention of therapeutic aerosols in the human lung, J Colloid Sci, 1947, *2*, 271.

(19) Hatch, T. F., and Hemeon, W. C. L.: Influence of particle size in dust exposure, J Industr Hyg, 1948, *30*, 172.

(20) Trurnit, H. J.: Some physical aspects of aerosol inhalation, Army Chemical Corps, Medical Division Report No. 181, 1949, p. 11.

(21) Davies, C. N.: Inhalation risk and particle size in dust and mist, Brit J Industr Med, 1949, *6*, 245.

(22) Landahl, H. D.: On the removal of air-borne droplets by the human respiratory tract: I. The lung, Bull Math Biophys, 1950, *12*, 43.

(23) Berghaus, H.: Das Abscheider elektrisch aufgeladener Aerosole in engen Röhren insbesonlere in der menschlichen Lunge, Aerosol-Forsch, 1953, *2*, 222.

(24) Eisenbud, M.: Retention, distribution, and elimination of inhaled particles, AMA Arch Industr Hyg, 1952, *6*, 214.

(25) Plenius, Caisus Secundus, *Naturalis historia Bk II* by K. C. Baily under the title *The Elder Pliny's Chapter on Chemical Subjects*, Part 1, Longmans Green & Co., 1929.

(26) Gessner, H., Ruttner, J. R., and Buhler, H.: Zur Bestimmung des Korngrossenbereiches von silikogenem Staub, Schweiz Med Wschr., 1949, *79*, 1241; 1258.

(27) Bedford, T., and Warner, C. G.: The size and nature of dust particles found in lung tissue, Brit J Industr Med, 1950, *7*, 787.

(28) Thomas, K., and Stegemann, H.: Darstellung dem Fremdstaübe aus Lungen and ihre Eigenschaften, Beitr. Sihkoseforsch, 1954, *28*, 1x.

(29) Moir, J.: General Report of the Miners Phthisis Committee, Union of South Africa, 1916.

(30) McCrae, P.: General Report of the Miners Phthisis Committee, Union of South Africa, 1916.

(31) Van Wijk, A. M., and Patterson, H. S.: The percentage of particles of different sizes removed from dust-laden air by breathing, J Industr Hyg, 1943, *22*, 31.

(32) Brown, J. H., Cook, K. M., Ney, F. G., and Hatch, T.: Influence of particle size upon the retention of particulate matter in the human lung, Amer J Public Health, 1950, *40*, 450.

(33) Lehmann, K. B., Saito, S., and Gfrörer, W.: Uber die quantitative Absorption von Staub aus der Luft durch den Menschen, Arch Hyg Bakt, 1912, *75*, 152.

(34) Lehmann, G. J.: The dust-filtering efficiency of the human nose and its significance in the causation of silicosis, J Industr Hyg, 1935, *17*, 37.

(35) Milburn, R. H., Crider, W. L., and Morton, S. D.: The retention of hygroscopic dusts in the human lungs, AMA Arch Industr Health, 1957, *15*, 59.

(36) Worth, G., and Schiller, E.: Staubretention in alveolären Lungenbereich: Bericht über die medizinishwissenschaftliche Arbeitstagung uber Silikose, Beitr Silikoseforsch, 1951, *18*, 77.

(37) Dautrebande, L., Cartry, D., von Kerkom, I., and Cereghetti, A.: Essai de prevention de la silicose, Union Miniere du Haut-Katanga (1954).

(38) Drinker, P., Thomson, M. R., and Finn, J. L.: Quantitative measures of the inhalation, retention, and exhalation of dusts and fumes by man, J Industr Hyg, 1928, *10*, 13.

(39) Baumberger, J. P.: The amount of smoke produced from tobacco and its absorption in smoking as determined by electrical precipitation, J Pharmacol, 1923, *21*, 47.

(40) Sayers, R. R., Fieldner, A. C., Yant, W. P., Thomas, B. G. H., and McConnell, W. G.: Exhaust gases from engines using ethyl gasoline, U. S. Bureau of Mines, Rept. Invest., 2661 (1924).

(41) Dautrebande, L., Beckmann, H., and Walkenhorst, W.: Studies on deposition of submicronic dust particles in the respiratory tract, AMA Arch Industr Health, 1959, *19*, 383.

(42) Sinclair, D., and LaMer, V. K.: Light scattering as a measure of particle size in aerosols: The production of monodispersed aerosols, Chem Rev, 1949, *44*, 245.

(43) Cauer, H., and Neymann, N.: Neue Untersuchungen auf dem Gebiete der Elektro-Aerosol Inhalation, Staub, 1953, *33*, 293.

(44) Neymann, N.: Verhutung der Staublunge, presented before 2. Internationale Staublungen-Tagung, Munster, November, 1953; cited by Dautrebande *et al.*

(45) Beckman, H.: Ritenzione delle particelle nalate nei polmoni degli animali da esperimento, presented before 2a Giornata internazionale di Aerosologia, June 3, 1954; cited by Dautrebande *et al.*

(46) Scott, K. G., Lantz, H. C., Axelrod, D., Crowley, J., and Hamilton, I. G.: Studies on the inhalation of fissionable materials and fission products and their subsequent fate in rats and in man, Plutonium, Project Record of the National Nuclear Energy Series MDDC-1276, 1946.

(47) Scott, K. G., Axelrod, D., Crowley, J., and Hamilton, J. G.: Deposition and fate of plutonium, uranium, and their fission products inhaled as aerosols by rats and man, Arch Path, 1949, *48*, 31.

(48) Barrett, H. M., Irwin, D. A., and Semmons, J.: Studies on the toxicity of inhaled cadmium, J Industr Hyg, 1947, *29*, 279.

(49) Verzar, F., Hügin, F., and Massion, W.:

Zurückhaltung atmosphärischer Kondensationskerne in den Atemwegen", Pflueger Arch ges Physiol, 1955, *261*, 219.

(50) Hatch, T. F., and Kindsvatter, V. H.: Lung retention of quartz dust smaller than ½ micron, J Industr Hyg, 1947, *29*, 342.

(51) Shoshkes, M., Banfield, W. G., and Rosenbaum, S. J.: The Distribution Effects, and Fate of Oil Aerosol Particles After Retention in the Lungs of Mice, Part IV, Medical Division Report No. 181, Army Chemical Center, Md., 1949.

(52) Asset, G., Gongwer, L. E., and Ryan, S.: Nasal penetration of particles of small inertia in experimental animals, AMA Arch Industr Health, 1956, *13*, 597.

(53) Punte, C. L., Jr.: Influence of particle size on inhalation toxicity of paraxon in rats, AMA Arch Industr Health, 1956, *13*, 352.

(54) Cohn, S. H., Lane, W. B., Gong, J. K., Sherwin, J. C., and Milne, W. L.: Inhalation and retention of simulated radioactive fall-out by mice, AMA Arch Industr Health, 1956, *14*, 333.

(55) Ishikawa, T., and Drinker, P.: Studies in dust retention: IV. Dust retained by tracheotomized cat, J Industr Hyg, 1933, *15*, 57.

(56) Wilson, H. B., Sylvester, G. E., Laskin, S., LaBelle, C. W., Scott, J. K., and Stokinger, H. E., Retention of particle size of U3O8 dust to toxicity following inhalation by animals, AMA Arch Industr Healtb, 1955, *11*, 11.

(57) Wilson, H. B., Silvester, G. E., Laskin, S., LaBelle, C. W., Scott, J. K., and Stokinger, H. E.: Relation of particle size of uranium dioxide dust to toxicity following inhalation by animals, AMA Arch Industr Hyg, 1952, *6*, 93.

(58) Morrow, P. E., and Gibb, F. R.: The deposition of submicronic aerosol in the respiratory tract of dogs, Amer Industr Hyg Ass J, 1958, *19*, 196.

MICROSCOPIC EXAMINATION OF BRONCHIAL EPITHELIUM IN CHILDREN[1, 2, 3]

OSCAR AUERBACH, ARTHUR PURDY STOUT, E. CUYLER HAMMOND, AND LAWRENCE GARFINKEL

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INTRODUCTION

In an extended study of a large number of adults, including smokers and nonsmokers and subjects with and without lung cancer, the writers have been convinced that persons who are cigarette smokers show changes in the bronchial mucosa which must be considered precancerous and which increase in amount depending upon an increase in the consumption of cigarettes. Adult nonsmokers may show a minimal amount of such precancerous changes. It seemed important to study a group of subjects who were nonsmokers and whose tracheobronchial trees had been subjected to a minimal amount of irritation from inhaled contaminants. Accordingly, a group of 35 children less than fifteen years of age were selected, and their tracheobronchial trees were studied. These children had died from various causes with and without pneumonia and bronchial ulceration. It was of special interest to learn whether or not any precancerous changes could be recognized and what had been the effects of pneumonia and bronchial ulceration on the bronchial mucosa.

The Bronchial Epithelium and Its Changes

The appearance of bronchial epithelium in any particular area may be described in terms of the following characteristics: the presence or absence of ciliated cells; the number of cell rows; the arrangement of cells, e.g., "normal," stratified layering, highly disorderly arrangement, et cetera; and the proportion of cells of each of the following types: normal appearing basal cells, squamous cells, enlarged vesicular cells, atypical cells, giant cells, and the presence of mitotic figures. Virtually every combination of these characteristics can be found if thousands of sections of bronchial epithelium from hundreds of different persons of various ages and exposures are examined.

The epithelium is considered to be "normal" under the following conditions: there is no loss of cilia, there are just one or two rows of basal cells, and no atypical cells are found. Sometimes enlarged vesicular cells are seen but this alone is not considered to be other than normal.

The epithelium is considered "changed" if it appears to be other than "normal" as defined above. An area of "changed" epithelium may be referred to as a "lesion" without doing undue violence to the dictionary definition of that term. A detailed record is made of all of the characteristics of each lesion found, e.g., presence or absence of cilia, number of cell rows, the proportion of cells of each specific type, et cetera. The thousands of lesions which have been observed can be divided into hundreds of different groups on the basis of various combinations of characteristics. It would be desirable to classify these groups in a logical, systematic order. However, this would require more knowledge than is presently available on the biologic significance of specific types of lesions or the etiologic or pathogenic relationship between lesions which differ in certain respects. Therefore, for this presentation an arbitrary system of classification will be used, the main virtue of which is that it is similar to the system used in the past with adults.

Lesions are first divided into two broad categories: cilia present; and cilia absent. Each of these two categories is then subdivided as follows:

Lesions with cilia present which are divided into the following three groups:

(*a*) Lesions with three or more rows of basal cells, but no atypical cells present. This may be called basal cell hyperplasia.

[1] From the Laboratory Service, Veterans Administration Hospital, East Orange, New Jersey; and the Statistical Research Section, American Cancer Society.

[2] Supported by a research grant from the American Cancer Society.

[3] Presented before the Medical Session, as part of *Section 7B*, at the annual meeting of the American Trudeau (now Thoracic) Society, Los Angeles, California, May 18, 1960.

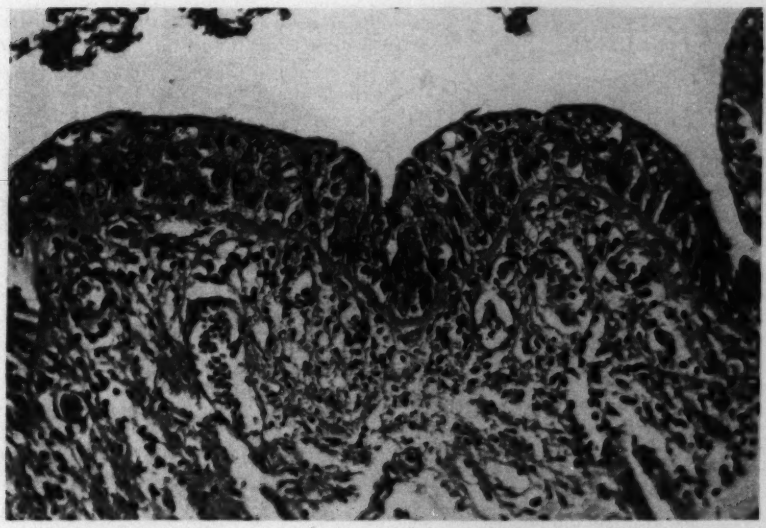

FIG. 1. Basal cell hyperplasia composed almost entirely of enlarged cells with large vesicular nuclei.

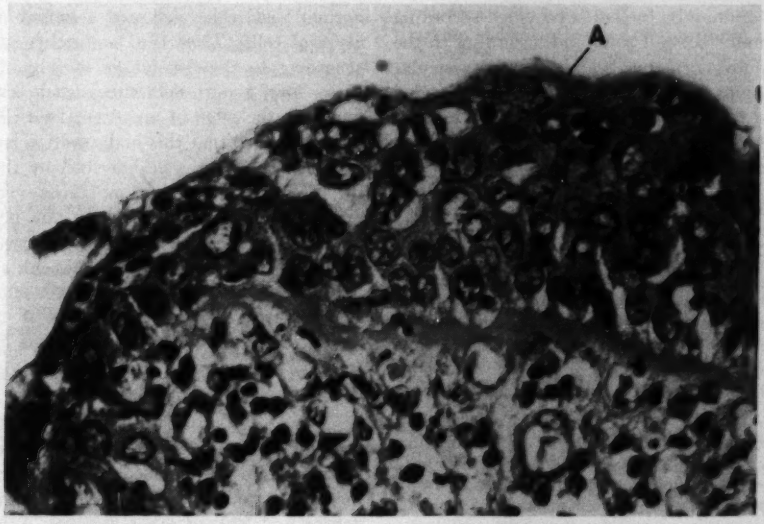

FIG. 2. High-power view of figure 1. Cilia are still present (*A*). Vesicular nuclei are particularly well demonstrated.

(*b*) Lesions with less than three rows of basal cells with some atypical cells present.
(*c*) Lesions with three or more rows of basal cells with some atypical cells present.

Enlarged vesicular cells may (figures 1 and 2) or may not be found in lesions of each of these three types, and a few flattened cells are sometimes present. For a more refined analysis, lesions

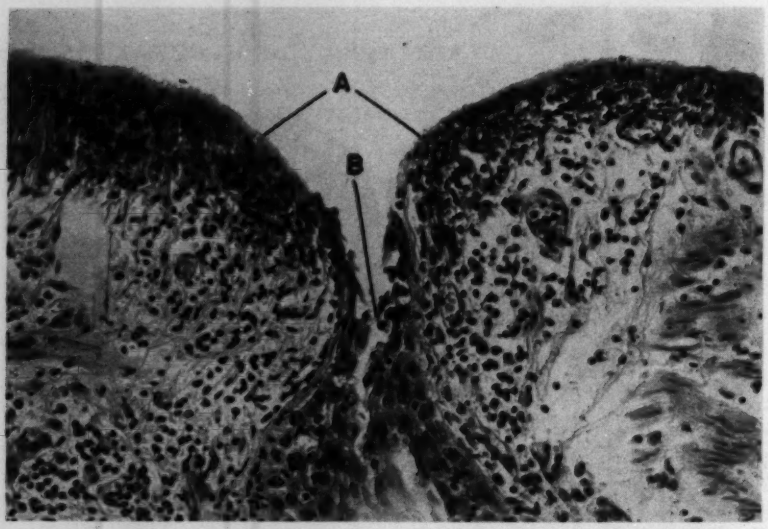

FIG. 3. Ulceration of bronchus (*A*) with regeneration of epithelium (*B*). There is a flattening of the superficial cells and a loss of cilia at the site of regeneration.

of type "*a*" may be further subdivided according to the number of cell rows and according to the proportion of normal cells and enlarged vesicular cells. Lesions of type "*c*" may be subdivided according to the number of cell rows and according to the proportion of normal cells, enlarged vesicular cells, and atypical cells.

Lesions with cilia absent which are first divided into the following four groups:

(*a*) Lesions consisting of a relatively thin layer of a few cell rows with flattening of cells on top. Some atypical cells may be present, but not all of the cells are atypical. This may be called stratification.

(*b*) Lesions consisting of a thicker layer of cells than described above with flattening of cells on top having the appearance of squamous cells seen in other tissues. Some atypical cells may be present, but not all of the cells are atypical. These lesions may be called squamous metaplasia.

(*c*) Lesions consisting entirely of atypical cells, but with no evidence of invasion. Giant cells and mitotic figures may or may not be present. These lesions generally fit the description of carcinoma-in-situ as defined by Black and Ackerman (1).

(*d*) Invasive carcinoma.

Lesions of types "*a*" and "*b*," as outlined above, have various proportions of flattened cells, normal basal cells, enlarged vesicular cells, and atypical cells. They can be further subdivided according to the percentage of cells of each of these four types. Sometimes such lesions are found at the edge of an ulcer (figure 3). For a time it seemed that this juxtaposition had special significance and it was described by the writers by the term "regeneration." However, on re-examining the sections, it was not possible to prove the existence of a difference between lesions at the edge of an ulcer and lesions not associated with an existing ulcer. Therefore, such a distinction is no longer made, and it is merely recorded whether or not the lesion is located at the edge of an ulcer.

Previous Work

In a previous study (2) 20,665 microscopic sections from the tracheobronchial trees of 402 men were examined, 63 of whom died of lung cancer and 339, of other diseases. A history of smoking habits and occupations was obtained for each of these subjects. The major findings may be described briefly as follows:

From men who never smoked regularly and who died of causes other than lung cancer, only 16.8 per cent of the sections showed some epithelial change. The most common type of lesion found in this group of subjects was basal cell hyper-

plasia with no atypical cells. Only a very small percentage of the sections had stratification or squamous metaplasia and only a small percentage had atypical cells. Not a single carcinoma-in-situ was found in this group.

In striking contrast, one or more epithelial changes were found in 99.8 per cent of the sections from men who died of lung cancer and 98.0 per cent of the sections from regular cigarette smokers who died of causes other than lung cancer. The proportion of sections with basal cell hyperplasia of 5 or more cell rows in depth, stratification, and squamous metaplasia increased rapidly with the amount of cigarette smoking. A large proportion of these lesions had atypical cells, the number of atypical cells increasing with the amount of cigarette smoking. The proportion of sections with carcinoma-in-situ rose from 0.3 per cent for men who smoked less than half a pack of cigarettes per day to 11.4 per cent for men who smoked two or more packs of cigarettes per day.

The major concern here is with the explanation of lesions found in the bronchial epithelium of nonsmokers who died of causes other than lung cancer. Three possible causative factors come to mind, namely: infections, exposure to air contaminants of one sort or another, and the effects of aging. It was thought that a study of bronchial epithelium in children might throw some light on this matter; hence the present study was conducted.

Material and Method of Study

The subjects were 35 children less than fifteen years old who were examined at autopsy in the following hospitals: Albany Hospital; Benedictine Hospital, Kingston; Kingston Hospital; St. Mary's Hospital, Troy; Columbia Memorial Hospital; Binghamton City Hospital; and St. Mary's Hospital, Amsterdam. The age and sex distribution of the children is shown in table 1. By a method previously described (3), the tracheobronchial tree was dissected out of the lungs of each subject and divided into 208 portions which were embedded in paraffin. One slide was prepared from each block. For this study, it was decided to examine 50 sections from each subject. The sections selected are indicated on the schematic diagram shown in figure 4. Potentially, there was a total of 1,750 sections (50 from each of 35 children), but 173 were missing due to technical difficulties. Thus, there were 1,577 sections available for examination.

TABLE 1

Distribution of 35 Subjects by Age and Sex

Age	Males	Females	Total
Less than 1 year	3	2	5
1 to 2 years	2	4	6
2 to 4 years	2	1	3
4 to 6 years	5	0	5
6 to 8 years	1	2	3
8 to 10 years	2	2	4
10 to 12 years	0	4	4
12 to 15 years	3	2	5
Total	18	17	35

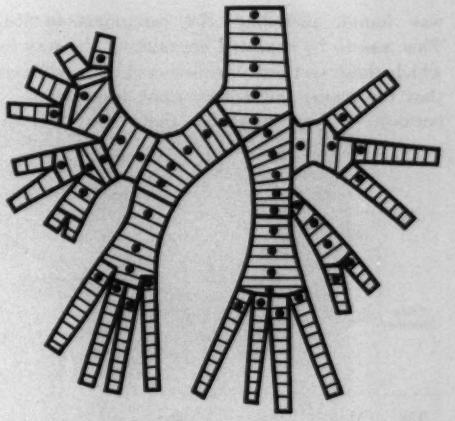

Fig. 4. Schematic diagram of the tracheobronchial tree. The circles indicate the locations from which 50 sections were selected for study.

In order to avoid any possibility of bias, it was decided that the sections from children should be mixed with sections from adults. A total of 1,656 sections was selected from small bronchial tubes of adults so that it would be difficult to distinguish them from larger sections from the lungs of children. The sections from adults had not been examined previously, but they were taken from cases in which large numbers of lesions had been found, i.e., heavy cigarette smokers who died of causes other than lung cancer. This was done in order to assure that every type of epithelial lesion would be represented in the sample.

The total set of 3,233 slides (1,577 from children plus 1,656 from adults) was then put in completely random order by means of random numbers. Serial numbers were placed on the slides while in this order. Therefore, the person who examined them had no way of knowing which came from children and which came from adults.

The senior writer read every slide himself. In addition, another of the writers (A. P. S.) read samples of slides every week during the study. The findings were recorded in exactly the same way as in the previous study (2).

Observations

Findings in Epithelium

In the sections from adults, every type of lesion described in the earlier part of this paper

was found, including 174 carcinomas-in-situ. This was to be expected considering the way in which these sections were selected. This showed that the reader did not overlook lesions simply because of his knowledge that many of the sections in the total sample were taken from children. Other than this, the findings in these slides from adults have no significance in this study.

Of the 1,577 sections from children, 28 were

TABLE 2

SUMMARY OF FINDINGS IN EACH OF 35 CASES

(1) Case Number	(2) Sex	(3) Age	(4) Total Number of Sections	(5) Sections with Epithelial Lesion(s): Total with One or More Lesions	(6) Sections with Epithelial Lesion(s): Lesions with Cilia Present	(7) Sections with Epithelial Lesion(s): Lesions with Cilia Absent	(8) Sections with Ulceration	(9) Underlying Cause of Death	(10) Pneumonia
928	M	4 years	50	0	–	–	0	Leukemia	–
968	F	10 years	43	0	–	–	0	Bronchopneumonia	++
975	F	20 months	40	0	–	–	0	Bronchopneumonia	++
990	M	4 months	44	0	–	–	0	Interstitial pneumonia	++
997	M	4 months	34	0	–	–	0	Interstitial pneumonia	++
A15	F	10 months	41	0	–	–	0	Tetralogy of Fallot	–
B95	F	11 years	47	0	–	–	0	Aplastic anemia	+
C08	M	8 years	48	0	–	–	1	Encephalitis	–
C27	M	4 years	43	0	–	–	0	Leukemia	+
C57	F	19 months	27	0	–	–	0	Bronchopneumonia	++
E91	F	6 years	38	0	–	–	1	Acute glomerulonephritis	+
F03	F	14 years	49	0	–	–	0	Hemangioblastoma	–
984	M	13 years	50	1	0	1	1	Lymphosarcoma	–
A43	M	8 years	45	1	0	1	1	Gun shot wound	–
A45	F	11 months	46	1	0	1	2	Bronchopneumonia	++
C13	F	6 years	40	1	0	1	1	Wilm's tumor of kidney	–
C43	M	4 years	48	1	0	1	1	Congenital stenosis of pulmonary valve	+
C63	M	7 months	40	1	1	0	0	Asphyxia (strangulation)	–
C69	M	3 years	28	1	0	1	1	Bronchopneumonia	++
974	M	18 months	49	3	2	1	3	Second-degree burns	+
979	M	18 months	46	3	0	3	3	Bronchopneumonia	++
D92	F	2 years	48	4	3	1	1	Laceration of liver	–
D53	F	10 years	50	5	0	5	8	Bronchopneumonia	++
A10	M	5 years	50	8	0	8	5	Encephalopathy	+
969	F	10 years	49	9	0	9	11	Acute encephalitis	+
929	F	9 years	50	10	1	9	13	Pneumonia	++
C44	M	7 years	44	10	0	10	27	Tuberculous meningitis	+
E95	M	12 years	49	14	2	12	12	Fractured skull	–
A13	M	3 years	44	15	14	3	1	Neuroblastoma	+
978	F	15 months	40	17	12	7	2	Staphylococcal pneumonia	++
982	F	14 years	49	22	1	22	28	Lymphosarcoma	–
A05	F	15 months	44	25	1	25	24	Bronchopneumonia	++
737	M	13 years	49	33	0	33	40	Fractured skull	–
A24	F	9 years	39	35	0	35	35	Disseminated lupus erythematosus	+
855	M	4 years	48	37	0	37	33	Astrocytoma	+
Total cases			1,549	257	37	226	255		

(4) Number of sections with some epithelium present
(9) Underlying cause of death based upon gross and microscopic findings at autopsy
(10) ++ died of pneumonia
+ pneumonia present at time of death but died of some other cause
– no evidence of pneumonia

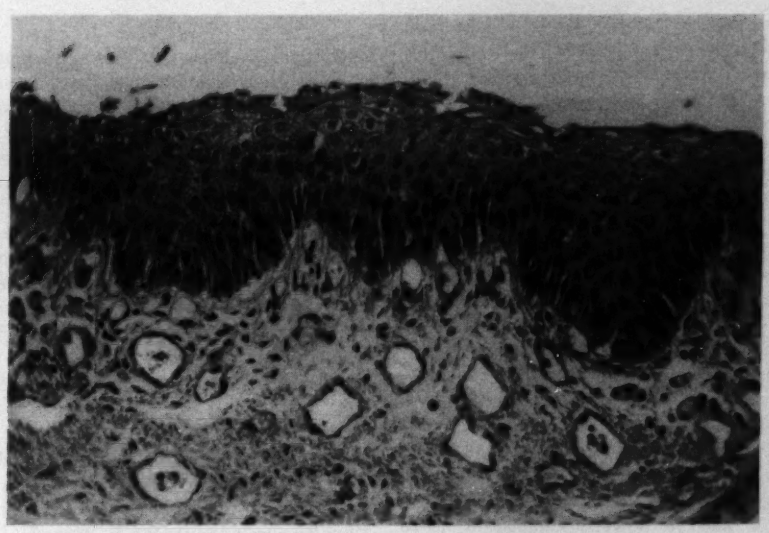

FIG. 5. Squamous epithelium is present over a large part of the surface.

completely denuded of epithelium, either because of complete ulceration or technical faults, leaving 1,549 in which epithelium was present for examination. Figures given hereafter are based on these 1,549 sections. The number per case varied from 27 to 50, the average being 44.3 per case for the 35 cases.

Not a single lesion resembling carcinoma-in-situ was found in the 1,549 sections from children. Furthermore, no atypical cells were found in any of these sections.

A summary of findings in each case is shown in table 2, the cases being arranged in order by the number of sections with epithelial lesions. Not a single epithelial lesion was found in sections from 12 of the 35 cases. In an additional 7 cases, only one lesion was found per case. In 6 of these 7 cases the single lesion was an area with cilia absent and in one case the lesion was an area with cilia present, i.e., basal cell hyperplasia.

From 3 to 37 sections with epithelial lesions were found in the remaining 16 cases. In a few instances, two or more lesions of different types were found in the same section. In most cases, the majority of lesions were areas with cilia absent, e.g., stratification and squamous metaplasia (figures 5 and 6), but in 4 cases the majority of lesions were areas with cilia present, i.e., basal cell hyperplasia.

The underlying cause of death is shown in column 9 of table 2, as determined from gross and microscopic findings at autopsy before this set of slides was examined. Whether or not pneumonia was present at the time of death is indicated in column 10. There appears to be no relationship between pneumonia at the time of death and the occurrence of lesions in the bronchial epithelium. Of the 12 patients with no epithelial lesions, 5 died of pneumonia, 3 others had pneumonia at the time of death, and 4 did not have pneumonia. Of 16 patients with three or more epithelial lesions, 5 died of pneumonia, 7 others had pneumonia at the time of death, and 4 did not have pneumonia. In one case (a 13-year-old boy who died of a fractured skull), 33 of 49 sections had lesions with cilia absent (stratification or squamous metaplasia) although there was no evidence of pneumonia at the time of death.

In each of three age groups, i.e., less than two years, two to eight years, and eight years and older, there were several patients with no epithelial lesions, and there were several with many lesions. However, the over-all percentage of sections with findings increased somewhat with age. Considering the small number of cases, this slight appearance of an age trend may well be due to chance. There is no indication of a sex difference in the occurrence of epithelial lesions in children.

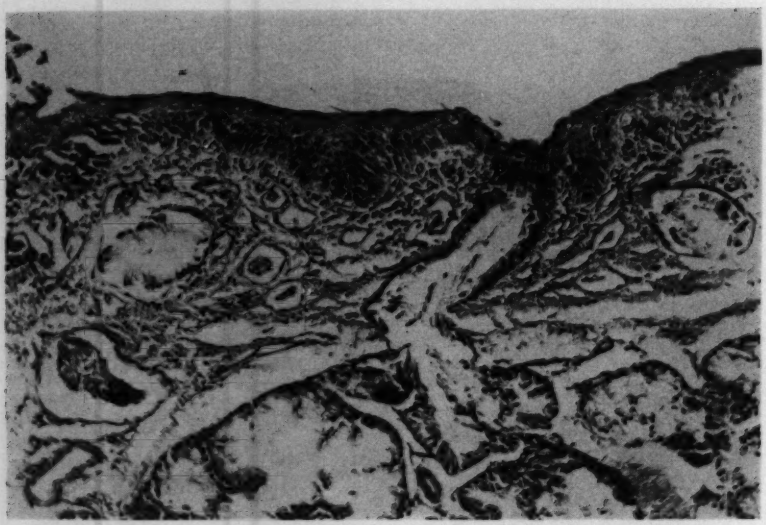

FIG. 6. Squamous epithelium lines the surface. The epithelium at the mouth of the duct is stratified while that in the depth is columnar in character.

Only 37 (2.4 per cent) of the 1,549 sections had epithelial changes characterized by 3 or more rows of cells below a layer of columnar cells with cilia present, i.e., basal cell hyperplasia. These 37 lesions may be further described as follows:

The lesions were found in only 9 of the 35 cases (14 were found in *Case A13* and 12 were found in *Case 978*). Twenty-nine of the lesions had an average of 3 rows of cells below the columnar layer and 8 had an average of 4 rows. Every one of them had some enlarged vesicular cells, the average below the columnar layer being 52 per cent enlarged vesicular cells and 48 per cent normal appearing basal cells. However, 12 had more than 60 per cent enlarged vesicular cells and 2 had less than 30 per cent. No atypical cells were found.

A total of 226 (14.6 per cent) of the 1,549 sections had epithelial changes characterized by absence of cilia. These occurred in 22 of the 35 cases. The number of such sections in these 22 cases ranged from 1 to 37. The lesions with absence of cilia found in these 226 sections may be further described as follows:

They were divided into two groups: a relatively thin layer of a few rows of cells with flattening on top, i.e., stratification, and a thicker layer of cells with flattening on top, i.e., squamous metaplasia (*see* figures 5 and 6). Lesions of both types are sometimes found in the same section. Sometimes they are in different parts of the section. Two or more separate lesions of the same type are often found in one section. When this occurs, a notation is made of the fact, but for this presentation the section was simply counted as having that type of lesion.

Of the 226 sections, 155 had stratification but not squamous metaplasia; 19 had squamous metaplasia but not stratification, and 52 had both stratification and squamous metaplasia. Thus, altogether there were 207 sections with stratification and 71 sections with squamous metaplasia. No atypical cells were found in any of these lesions. Enlarged vesicular cells were found in all but one of these lesions. In the 207 zones of stratification, an average of 51.1 per cent enlarged vesicular cells was found (49 had more than 60 per cent enlarged vesicular cells and 10 had less than 30 per cent enlarged vesicular cells). In the 71 zones of squamous metaplasia, an average of 60.8 per cent enlarged vesicular cells were found (32 had more than 60 per cent enlarged vesicular cells and none had less than 30 per cent).

Ulceration

The underlying tissue as well as the epithelium of each section were examined for evidence of ulceration. All gradations were found from well-defined ulcers to the vestiges of nearly healed ulcers (*see* figure 3). A total of 256 sections with one or more ulcers was found among the 1,549 sections with some epithelium present. These were in sections from 24 of the 35 cases as shown in column 8 of table 2. An additional 6 sections with ulceration were found among the 28 sections which were completely denuded of epithelium. For the sake of simplicity, these 6 have been omitted from table 2, and figures which follow since their inclusion would not alter any of the statements made hereafter.

There appears to be no relationship between the finding of ulceration and the presence or absence of pneumonia at the time of death.

A study was made of ulceration in relation to epithelial changes of the types previously described. Of the 1,549 sections, 1,245 (80.4 per cent) had neither ulceration nor epithelial changes; 209 (13.5 per cent) had both ulceration and one or more epithelial changes; 47 (3.0 per cent) had ulceration but no epithelial changes; and 48 (3.1 per cent) had epithelial changes but no ulceration. In other words, of 256 sections with ulceration, 209 (81.6 per cent) had epithelial findings; and of 1,293 sections without ulceration, only 48 (3.2 per cent) had epithelial changes. From this it is evident that, in this set of sections from children, epithelial changes were highly associated with ulceration. However, no association was found between ulceration and basal cell hyperplasia. Only 2 sections with ulceration were found among the 37 sections with basal cell hyperplasia; and in these 2 sections the areas of basal cell hyperplasia were not adjacent to the ulcers.

Discussion

The findings in the bronchial epithelium of 35 children were similar to previous findings in the bronchial epithelium of 65 adult males who never smoked regularly and died of causes other than lung cancer (2). In the majority of subjects of both groups, few or no changes were found in the bronchial epithelium. Some epithelial change was found in 16.8 per cent of 3,324 sections from the 65 adults and some epithelial change was found in 16.6 per cent of 1,549 sections from the 35 children. The main differences were as follows: more basal cell hyperplasia was found in the adults than in the children; more lesions characterized by the loss of cilia were found in children than in the adults; and some atypical cells were found in some of the sections from the adults, while no atypical cells and no carcinomas-in-situ were found in any of the sections from the children. Altogether, the differences between children and nonsmoking adults were so slight as to suggest that the aging process per se has little or no influence on the occurrence of lesions in bronchial epithelium.

The scarcity of changes in the bronchial epithelium of children and of adults who never smoked regularly is in striking contrast to the large number of changes (including carcinoma-in-situ and large numbers of atypical cells) found in the bronchial epithelium of heavy cigarette smokers (2). It is possible that changes found in the bronchial epithelium of some adult nonsmokers (and perhaps changes found in a few of the children) were due to exposure to air pollutants of one sort or another, e.g., dust, vapors, pollen, et cetera.

In children, there is a very high degree of association between ulceration and the occurrence of epithelial lesions characterized by the absence of cilia. The appearance of these lesions suggests that they represent a healing process following ulceration. However, some such changes were found not in association with an existing ulcer. Conceivably these resulted from a pre-existing ulcer which had disappeared; but this is by no means certain. It could also be that such changes sometimes occur entirely independently of ulceration.

Before the start of this study, the hypothesis was considered that changes in bronchial epithelium might be produced by pneumonia. The findings do not support this hypothesis since, in the 35 children studied, no association was found between changes in bronchial epithelium and the presence of pneumonia at the time of death. However, this does not exclude the possibility that some of the epithelial changes found were produced by unidentified respiratory infections.

Summary

The epithelium of 1,549 sections of the tracheobronchial tree of 35 children showed no atypical

cells in any of the sections nor a single lesion resembling a carcinoma-in-situ.

Epithelial changes were found in 16.6 per cent of the 1,549 sections. This compares with 16.8 per cent of sections of adults who never smoked regularly. The epithelial changes in children were those chiefly of squamous metaplasia and stratification (14.6 per cent) and only 2.4 per cent were those of basal cell hyperplasia. In adults, 6.0 per cent of the sections showed squamous metaplasia and stratification and 9.4 per cent showed basal cell hyperplasia. The reasons for this difference may lie in the fact that the majority of lesions in children appear to be the result of the repair of ulcers.

In this series of children studied there appears to be no relationship between ulceration and pneumonia at the time of death.

Sumario

Examen Microscópico del Epitelio Bronquial en los Niños

En 35 casos, el epitelio de 1,549 cortes de los árboles tráqueobronquiales no reveló células atípicas en ninguno de los cortes ni una sola lesión parecida a carcinoma-in-situ.

Se observaron alteraciones epiteliales en 16.6 por ciento de los 1,549 cortes. Esto se compara con 16.8 por ciento de cortes de sujetos adultos que jamás fumaron con regularidad. Las alteraciones epiteliales en los niños consistieron principalmente en metaplasia y estratificación escamosas (14.6 por ciento) y sólo en 2.4 por ciento fueron las de la hiperplasia baso-celular. En los adultos, 6.0 per ciento de los cortes revelaron metaplasia y estratificación escamosas y 9.4 por ciento hiperplasia basocelular. Las razones de esta diferencia quizás dimanen de que la mayoría de las lesiones en los niños parecen ser consecuencia de la regeneración de úlceras.

En esta serie de niños, no parece que haya habido relación entre la ulceración y la neumonía en el momento de la muerte.

Resume

Examen microscopique de l'epithelium bronchique chez des enfants

L'epithelium de 1.549 coupes d'arbres trachéobronchiques, dans 35 cas, ne montra pas de cellules atypiques dans aucune des sections, et ne montra pas non plus une seule lésion ressemblant à un carcinome in situ.

On trouva des changements epithéliaux dans 16,6% des 1.549 coupes. Ceci se compare à 16,8% de coupes d'adultes qui ne fumaient pas régulièrement. Les changements épithéliaux chez les enfants furent principalement ceux de métaplasie squameuse et de stratification (14,6%), et seulement 2,4% consistèrent en une hyperplasie des cellules basales. Chez les adultes, 6,0% des coupes montrèrent une métaplasie squameuse et une stratification, et 9,4% montrèrent une hyperplasie des cellules basales. Les raisons de cette différence pourraient reposer dans le fait que la majorité des lésions chez les enfants semblant être le résultat de la réparation d'ulcération.

Dans ces séries d'enfants étudiés, il semble qu'il n'y ait pas de rapport entre l'ulcération et la pneumonie au moment de la mort.

REFERENCES

(1) Black, H., and Ackerman, L. V.: Importance of epidermoid carcinoma-in-situ in histogenesis of carcinoma of lung, Ann Surg, 1952, *136*, 44.

(2) Auerbach, O., Stout, A. P., Hammond, E. C., and Garfinkel, L.: Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. (Abridgement of this paper was read at the Clinical Meeting of the American Medical Association, Dallas, Texas, December 4, 1959.)

(3) Auerbach, O., Gere, J. B., Forman, J. B., Petrick, T. G., Smolin, H. J., Muehsam, G. E., Kassouny, D. Y., and Stout, A. P.: Changes in the bronchial epithelium in relation to smoking and cancer of the lung, New Engl J Med, 1957, *256*, 97.

GROWTH OF ASPERGILLUS IN THE HUMAN LUNG[1, 2]

Aspergilloma and Aspergillosis

N. G. M. ORIE, G. A. DE VRIES, AND A. KIKSTRA

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INTRODUCTION

The existence of pulmonary lesions which contain growths of Aspergillus has been known for a long time. The older French writers attributed this affection to contact with pigeons (*gaveurs des pigeons*), while great importance was also attached to the carding and combing of wool (1, 2). Later, however, this infection (even though prevalent in this group of workers) was also detected in patients with quite other occupations. The fact that Dieulafoy (3) dedicated ten pages of his well-known *Manuel de Pathologie Interne* to this infection, and only four pages to bronchial carcinoma, demonstrates how important aspergillosis was considered in those times.

After having been forgotten for some time (4), the infection again became a topic of interest in recent French literature (5–16) as well as in the English literature (17, 19, 20). In the American literature only an occasional communication is to be found, the clinical entity either being omitted (as in several textbooks (21) or only very briefly mentioned (22)). According to Conant (23), "primary pulmonary aspergillosis is rare and difficult to diagnose until necropsy." Rubinstein (24), on the other hand, gives ample attention to it. He writes that primary pulmonary growths are rare, but states that this disease is often associated with other pulmonary diseases. A great number of cases have been published also in the Netherlands and Belgium (25–31).

CLINICAL PICTURE

The following clinical pictures have been described (Hinson (32) gives many details from the literature).

One is the classical aspergilloma (33), which is a focus in the lung characterized by the so-called "crescent" (figure 1). Such a focus is sometimes isolated; sometimes it forms part of a more or less diffuse, bilateral, or unilateral fibrotic process of known (old tuberculosis or Besnier-Boeck-Schaumann's disease) or unknown nature. The isolated focus especially is no rare occasional finding.

Often an hemoptysis, which is considered characteristic, gives rise to the detection. Other concomitant bacterial infections of the respiratory passages do not exist as a rule.

Perhaps cases without typical aspergilloma are more frequently seen, in which aspergilli are found in the sputum, in operation specimens, or post mortem in a pulmonary focus; or cases in which Aspergillus is suspected on the basis of the morbid-anatomic picture. Here also, there are localized processes as well as local masses in more or less scattered lesions. Sometimes the process develops behind a bronchial stenosis.

Empyemas from which aspergilli are isolated, mixed or not mixed with other microorganisms, are observed once in a while, probably as a result of spilling of the content of an aspergillus-filled cavity.

Cases have also been described in which a white mass is observed after pulmonary resection, on bronchoscopy in a bronchial stump; on examination this mass proves to consist of a fungous growth from which aspergilli can be cultured.

Cases occur in which a miliary picture or septicemia is found and in which aspergilli can be isolated from the blood or from the tissues. Sometimes the infection results in a meningitis, and the fungus is cultured from the cerebrospinal fluid.

In some cases Hinson and co-workers regard the clinical picture, consisting of coughing, bronchitis, dyspnea, and sometimes asthma, as a result of sensitization to fungi growing on the body.

At one time Sayers and Merriwether (34) described a miliary calcification caused by Aspergillus. This observation has never been confirmed in later publications.

The microbial species found after adequate isolation and identification is almost always *Aspergillus fumigatus* Fres. This is not always the case, however, and it has sometimes been shown, in local as well as in diffuse processes, that the mycelia originated from other Aspergillus species (*Aspergillus amstelodamii*, *Aspergillus niger* (31), or from other fungi (Mucor, Penicillium).

[1] From the Division of Pulmonary Diseases of the Medical Clinic of the State University of Groningen; and the Department of Medical Mycology of the Centraal Bureau voor Schimmelcultures, Baarn, Holland.

[2] Supported by a grant from the National Research Council T. N. O.

FIG. 1. Typical aspergilloma (resection).

This occurs so rarely, however, that the presence of *Aspergillus fumigatus* can be suspected with a reasonable degree of probability only on the basis of the microscopic picture, i.e., the finding of mycelial masses.

Although sexual sporulating species are known of the genus *Aspergillus Micheli*, the majority of the species still belongs to the fungi imperfecti. *Aspergillus fumigatus* Fres is mainly characterized by one row of sterigmata, an only partially "overgrown" vesicula, and by the size and the form of the spores (figure 2). The latter, which are at first colorless but then change to green and light gray via a bluish intermediate hue, are decisive for the color of the colonies. For details of the hundreds of species, the reader is referred to Thom and Raper (36). The schema, given by these writers, is represented in figure 3.

OBSERVATIONS

The series of patients reported consist of 22 cases observed by one of the writers (N.G.M.O.)[3] and of 29 other cases, recognized and treated elsewhere[4]; as in the first 22 cases, the mycologic diagnosis of the fungi of the second group was established by one of the writers (G.A. de V.).

The series is subdivided into two groups because it was impossible to obtain equally extensive data from all patients (partly due to imperfections in the questionnaire form, which otherwise was filled in with great care). Great differences between the two groups did not become manifest.

The existence of an Aspergillus growth was verified in 51 cases. In most of them, it was established—or was very probable—that this growth had actually taken place in the lung.

The data regarding sex, age, complaints, "source of infection," and the presence and the nature of pre-existent or concurrent pulmonary disease, if any, are presented in table 1. In table 4, the data on the pre-existing lesion are presented in another way.

Clinical Findings

In 15 cases of hemoptysis it was reasonable (but not necessary) to attribute this only to the fungous growth. For the rest, with two excep-

[3] Including 5 cases in the Beatrixoord Sanatorium in Appelscha. The writers wish to thank Professor Kraan for his kindness in permitting the use of these data.

[4] The 29 cases were reported by Drs. G. Bauer, A. E. Beute, W. Bronkhorst, W. F. Carsjens, L. van der Drift, C. A. Graafland, A. M. W. Hekking, K. Magnus, B. J. Mansens, F. H. Meyer, J. Muller, J. G. Roosenburg, P. Ruitinga, and H. Vos.

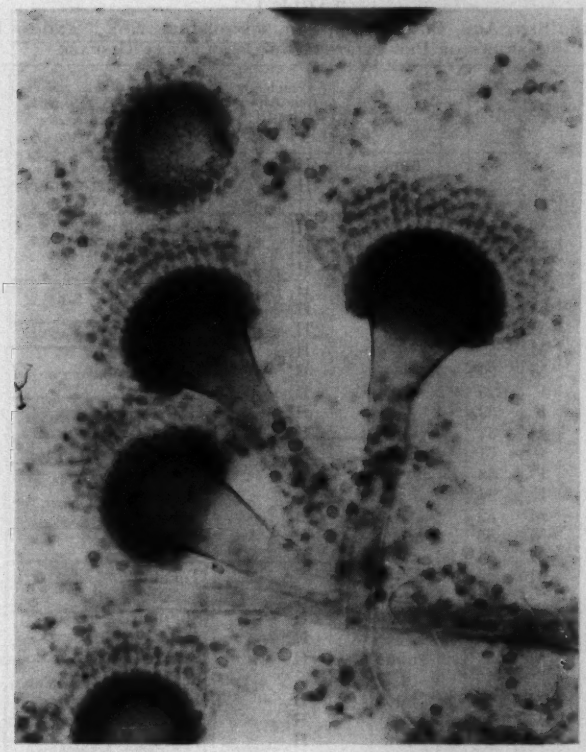

FIG. 2. Growth of *Aspergillus fumigatus* in hanging drop stained with cotton blue.

tions, there were no manifestations which could not be ascribed to pre-existent changes. The two exceptions were: first, the cerebral manifestations in patient *No. 9* which were doubtless due to the Aspergillus "metastases" and not to supposed metastases of a bronchial carcinoma (figure 4). The second exception was represented by case *No. 31*, and it was only in this case that the diagnostic methods were of no help. In this 25-year-old man, who fell acutely ill with a clinical and roentgenographic picture of miliary dissemination in the lung and who died after a fortnight, no other microbial cause was found than *Aspergillus fumigatus*, which was cultured both from the sputum and from the lung after autopsy. As no other cause was found, a primary role of the microorganism seemed reasonable.[5]

The local picture (*calotte aerienne*) (5, 25–27, 33) was no different from those published earlier. Sometimes there was no typical roentgenographic picture, but the proof was rendered by repeated sputum cultures or by the occurrence of a spontaneous pneumothorax with Aspergillus growth in the pleural cavity, or by an autopsy. On three occasions (in 22 cases) no aspergilli were demonstrated in the sputum culture despite the certainty (via surgery) that an aspergilloma existed. Moreover, when the sputum culture was positive, the direct preparation was always negative (periodic acid-Schiff staining, 22 ×). It should be emphasized that the "typical" aspergilloma may also be found in tuberculous patients, without Aspergillus growth.

Mycology

Isolation of fungus: The way in which fungous growth is demonstrated may be seen in tables 2 and 2*a*.

Although growth of Aspergillus in the lungs has often been described, some points have not

[5] This case will be published in full by Drs. Graafland and Beute.

TABLE 1

DATA REGARDING SEX, AGE, COMPLAINTS, "SOURCE OF INFECTION," AND OF PRESENCE OR NATURE OF PRE-EXISTENT OR CONCURRENT DISEASE

Number	Name	Sex	Age	Complaints	Complaints from Aspergillus (H = Hemoptysis)	Profession	Coexistent Diseases*
1	Dr.	M	45	none	H. +	Chauffeur	Br.
2	Ba.	F	27	none	H. +	Housewife (teacher)	Tbo. ?
3	Jo.-K.	F	63	+	H. −	Housewife	D. †
4	He.	M	54	+	H. −	Technician	D. (RB?)
5	St.	M	52	+	H. −	Draughtsman	B.B.
6	Vo.	M	36	+	H. ?	Smith	B.B.-Bronch.-E.
7	Am.	F	47	+	H. (2×)	Flower shop	Tbo ?
8	Dr.	M	82	+	H. ?	None	Bronch ?†
9	Bo.	M	49	+	H. −	Truck driver	Bronch†
10	Hess.	M	56	+	H. −	Chauffeur	Ca.†
11	Bui.	M	20	+	H. −	Draughtsman	Tb.
12	v. Wa.	F	±25	none	H. −		Tbc. S.
13	A. d. V.	F	33	+	H. +	Housewife	Bronch.
14	Kr.	M	37	+	H. +	Metal Worker	Bronch.
15	B.-O.	F	61	none	H. −		
16	Ad.	F	58	+	H. −	Teacher	Bronch.
17	Ko.	F	34	+		Housewife	Tb. S.
18	Hou.	M	32	+	H. −	Baker	Bronch.
19	Ste.	M	55	none	H. −	Shoe-shop	Tb.
20	Br.	M	38	none	H. −	Farmer	Tb.
21	K. Ha.	M	42	+	No ? H.	Teacher	Tbo. (BB) Bronch.
22	P. v. d. K.	M	40	none	H. −	Shepherd	Tb.
23	B. Ho.	F	38	+	H. −	Typist	B. B.
24	A. H. Me.	M	50	none	H. −	Factory director	Bronch.
25	P. Bo.	F	45	?	?	Sailor	E. Tb.
26	S. H. Wo.	M	23	none	H. −	Ladys help	E. Tb.
27	R. Fe.	M	36	+	H. −	Farmhand	Bronch.
28	H. Cr.	M	34	few	H. +	Farmer	Tbo. (PA)
29	M. Verw.	M	69	none	H. −	Farmer	?
30	E. T. Br.	F	70	+	H. +	No	D.†
31	H. v. d. B.	M	25	dyspnea fever	H. −	Shop employee	†
32	S. v. W.	M	48	few	H. +	Barber	Tb.
33	F. v. Heu.	F	23	+	H. −	Shop employee	E. Tb.
34	J. W. Ma.	M	40	+	H. +	Factory worker	Bechterew
35	B. W. Re.	M	32	+	H. +	Custom officer	Pa.
36	W. Fr.	M	17	−	H. −	School boy	—
37	F. v. d. W.	M	59	−	H. −	Help of veterinarian surgeon	—
38	C. d. Jo.	M	42	+	H. −	Fruitshop	
39	Mie.	F		?	H. +	?	?
40	v. d. Hoe.	F	20	+	H. −	Typist	Tbo. Bronch.
41	C. ve.	M	30	+	H. −	Farmhand	Tbo. Bronch.
42	v. Str.	M	43	+	H. +	Railway worker	Bronch.
43	St.	F	22	− (+)	H. −	Pedicure	(Bronch ??)
44	L. Ko.	M	57	+	H. −	Marketman	Bronch.
45	A. Bij.	M	39	+	H. −	Homeworker	Bechterew
46	H. Eng.	F	59	+	H. −	Housewife	D.
47	G. Wie.	M	33	± (cough)	H. −	Railway employee	Tbo. S.
48	Pe.	M	60	+	H. +	Farmhand	Tbo.
49	v. d. B.	F	36	+	H. −	Sewing woman	Bronch.
50	A. Gr.	F	56	± (cough)	H. −	Housewife	E.
51	J. W. R.	M	37	± (cough)	H. +	Draughtsman	Tb.

* Br. or Bronch. = bronchitis, bronchiectasis
Tb = tuberculosis

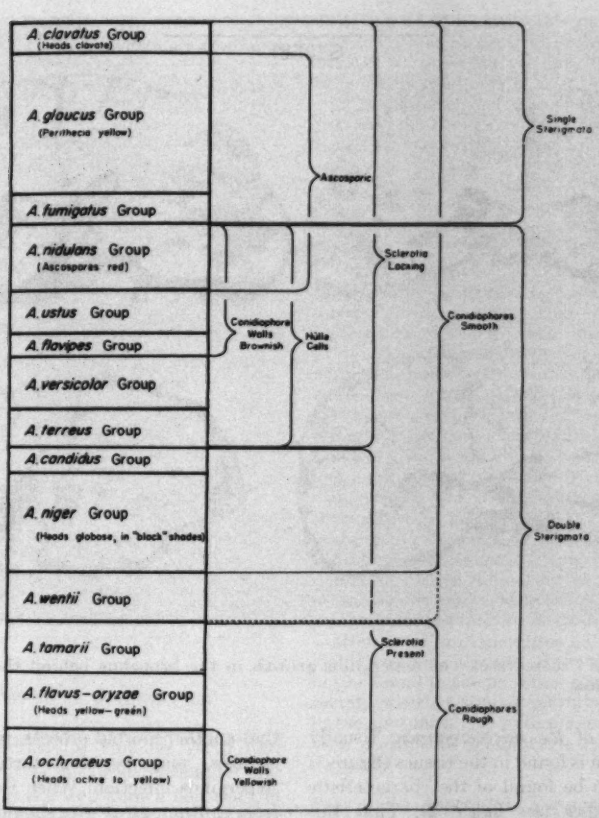

FIG. 3. Schema of aspergilli (*Used with permission of Drs. C. Thom and K. Raper from Manual of Aspergilli, published by the Williams & Wilkins Company, Baltimore, in 1945*).

been fully elucidated. The best method to prove the presence of the fungus in a lung lesion is not yet firmly fixed. Once the fungous growth is an established fact, there is no certainty whether it should be considered a primary or a secondary infection. If it be considered as only a secondary infection, it may still be producing inflammation or it may be merely a saprophytic growth. There is insufficient information on the influence of previous antimicrobial therapy on the pathogenesis of these infections.

It has not yet been established whether sensitization against Aspergillus can also be caused by growth of the fungus in the body, apart from sensitization by inhalation of the spores from the air

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Tbo = arrested tuberculosis
D = bilateral fibrosis or cyst
† = died
B.B. = Morbus Besnier Boeck Schaumann
Tb S or Tbc S = resection with stump lesion
E = empyema
Pa = pancytopenia
Ca = bronchogenic carcinoma
+ and − in complaints column means that symptoms originating from a different primary disease were present or absent.

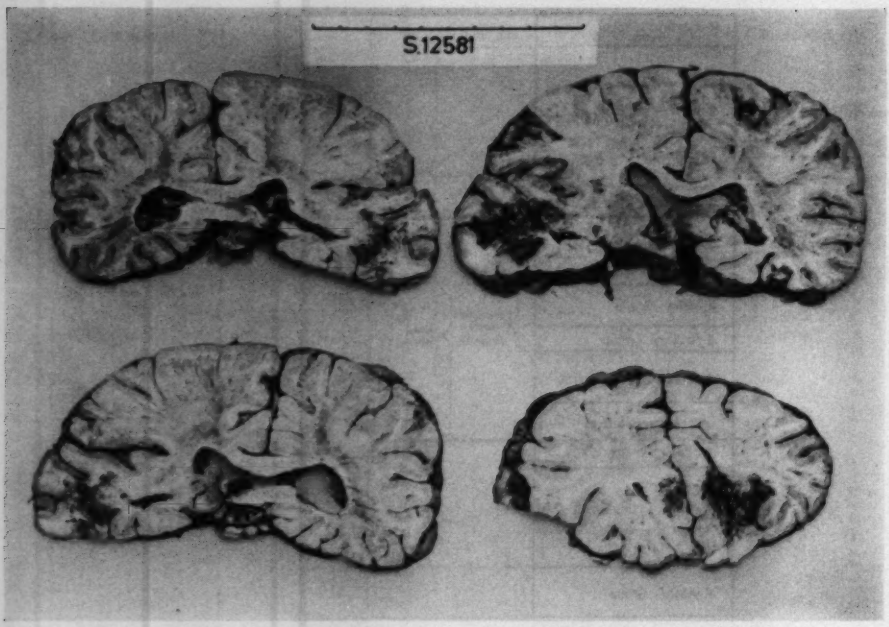

FIG. 4. Cerebral "metastases" of Aspergillus growth in the bronchus behind the obstruction of a bronchial carcinoma.

Demonstration of the microorganism: Usually only the mycelium is found in the tissues (figure 5) and nothing is to be found of the characteristic spore-bearing bodies (*see* figure 2). That this sometimes is the case is probably associated with the availability of more oxygen, e.g., communication with the main bronchi.

Culture is therefore always necessary to verify the nature of a fungus with certainty, just as this is always necessary to determine the species (3b) (*see* figure 3).

Growth on the nutrient medium (Sabouraud blood agar–malt agar) often does not develop until after about five days, so that it may easily be overlooked in the usual period of observation, especially in sputum cultures. (At 37°C. the growth takes place faster.) In general, the presence of fungi in the process can be proved by its isolation if this isolation takes place with cerebrospinal, blood, or pleural fluid. Isolation from a focus in an operation specimen can, in general, also be considered proof, that is, if the fungi are demonstrable both in the tissue sections and by culture. This does not exclude the possibility that another morbid process, for example, airway stenosis, may be the starting point of the Aspergillus infection. When isolating the fungus from sputum, great care should be observed (37). In order to have perspective on the relative significance of these isolates (contamination with buccal flora, as may occur in the isolation of yeasts (38)), it is, of course, of great importance to know how frequently *Aspergillus fumigatus* occurs outside and inside the human body.

With respect to the frequency outside the human body: *Aspergillus fumigatus* occurs with particular frequency in soil containing appreciable amounts of organic material, upon vegetable matter undergoing slow decomposition and upon imperfectly dried, stored grain (36). One of the present authors (G. A. de V.) found the fungus to be a common inhabitant of mouldy hay He further isolated it from air in three of five houses by means of the culture plate technique. He could not establish the frequency of this mould in open air because sufficient data were not yet obtained. *Aspergillus fumigatus* is probably more frequent in air than air-sampling data

TABLE 2

METHOD OF DEMONSTRATION OF FUNGOUS GROWTH

	Sputum Preparation	Sputum Culture	Culture of Operation Specimen	Roentgenogram	Pathologic Anatomy
1	−	−	+	+	+
2	−	−	+	+	+
3	−	−	+	+	0
4	−	+	+	+	0
5	0	0	0	+	0
6	−	+	+	−	0
7	−	+	0	−	0
8	−	−	0	+	0
9	−	0	0	−	+
10	−	0	0	−	+
11	0	0	+	+	+
12	−	+	0	±	0
13	−	+	+	+	0
14	−	+	0	+	0
15	−	+	0	−?	0
16	−	+	+	−	+
17	−	+	0	−	0
18	−	+	0	−	0
19	−	−	+	+	+
20	−	+ (bronchoscopy)	0	±	0
21	−	+	0	−	−
22	−	−	−	+	0

+ = positive
− = negative
0 = not investigated

such as those obtained by Van der Werff (39) would indicate. Besides this occurrence in air and on plant material, it is a well-known fact that, in apparently healthy animals and particularly in birds, *Aspergillus fumigatus* is frequently found, especially in the air bladder. The situation in the healthy or diseased human body (particularly in the mouth) has not been investigated sufficiently. A preliminary investigation yielded the findings set forth in table 3.

When examining the sputum for *Aspergillus fumigatus*, one is at a disadvantage as compared with the search for other microorganisms, bacteria particularly, because frequently the fungus cannot be recognized in the direct preparation. It is therefore impossible to decide from the sputum preparation by "washing" whether the fungi found in the culture originate from the oral cavity or from the real bronchial secretion (37, 38, 40). This is in contrast to yeasts, in which it is almost always possible to verify the origin of the fungi cultured (38).

On the other hand, the fact that *Aspergillus fumigatus* seldom occurs in the mouth of normal subjects and patients, in contrast to the situation with yeasts (41, 42), constitutes an advantage. Isolation at 37°C. with the addition of penicillin to the culture medium is probably advantageous because it prevents the growth of a number of other fungi which might occur as contaminants as well as of a number of bacteria. With the same precautions, however, the growth at 20°C. is equally often positive if perhaps somewhat slower to appear.

The situation of these fungi with respect to their presence in air sampling is as follows:

Candida albicans is never—and *Aspergillus fumigatus* is relatively frequently—found in the air and in house dust.[6] There are carriers in the animal kingdom of both microorganisms (41, 43–45). Sometimes there does not exist any permanent communication with the bronchus in proved cases of aspergillosis, and the cultures are therefore negative (cases *Nos. 1*, *2*, and *4*). It is further remarkable that occasionally, even when the fungous growth has clearly been demonstrated by many correct sputum cultures, it is impossible to demonstrate the fungi microscopically in the sputum (cases *Nos. 5*, *6*, *7*, *13*). This phenomenon is occasionally also observed when examining the contents of the aspergilloma cyst (case *No. 2*). Sometimes these difficulties can be overcome by using the periodic-acid-Schiff staining method, as known from the morbid anatomy (46).

Mixture of an Aspergillus culture with sputum yields excellent pictures of the spores which could not be found in the patients' sputum. It is not yet certain whether similar pictures can be obtained in the sputum of the patients, and thus far it has been possible to demonstrate the microbe in this way only once.

Role of the Aspergillus Fumigatus in the Pathogenesis of the Lesions from Which the Fungus Is Grown

It is possible to gather from the literature a number of cases of aspergillosis in which the infection seems to represent the primary disease. It is obviously not possible, in retrospect, to decide with certainty whether this was actually the case. It is quite certain that many cases are combined with a pre-existent disorder; for example, Besnier-Boeck-Schaumann's disease or old tuberculosis, in the case of a local growth of *Aspergillus fumigatus* or leukemia, carcinoma, or another serious disease, in cases in which generalization has occurred.

Comparison of the situation with other "deep" mycoses shows that histoplasmosis and, espe-

[6] With due precautions (meticulous care of the laboratory by daily cleaning with formaldehyde), contaminations in the laboratory should not occur even if *Aspergillus fumigatus* is regularly handled.

TABLE 2*a*

SUMMARY TABLE OF THE RESULTS OF THE DEMONSTRATION OF ASPERGILLUS FUMIGATUS IN THE CASES DESCRIBED

Sputum Preparation				Sputum Culture			Culture Operation Specimen			Roentgenogram			Pathologic Anatomy		
22.	22−	0+	0 Ø	6−	12+	4 Ø	1−	9+	12 Ø	6−	10(13)+	3 Ø	1−	7+	14 Ø
29.	?	0+	?	3−	23+	3 Ø	1−	8+	20 Ø	15−	9+	5 Ø	0−	9+	20 Ø
51.	?	?	?	9−	35+	7 Ø	2−	17+	32 Ø	21−	19(22)+	8 Ø	1−	16+	34 Ø

+ = positive; − = negative; Ø = not investigated or not considered

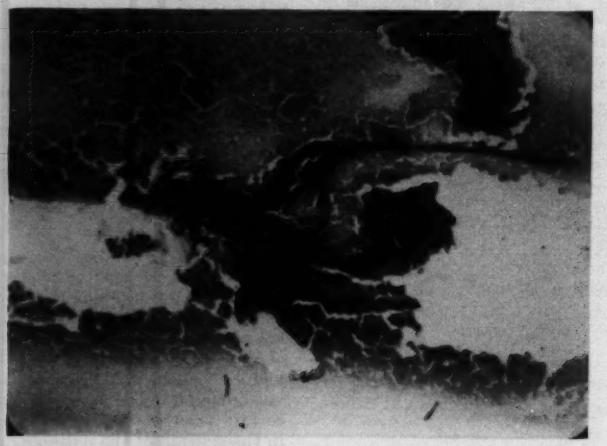

FIG. 5. *Aspergillus fumigatus*. Mycelium in aspergilloma after resection. Few threads in detritus. (100×)

cially, coccidioidomycosis are rather frequent and, like tuberculosis, are regarded as entirely primary affairs. In general, the same is true for cryptococcosis (torulosis). Despite the very low frequency of this infection (47), it is usually regarded as representing a primary disease. Sirven and co-workers (48), however, have called attention to the concurrence of cryptococossis with mesenchymal tumors.

With regard to infection with Candida (moniliasis), on the other hand, the frequent milder infections (aphthae, vaginal apthae, esophagitis), as well as the very rare pulmonary, meningeal, and septic forms, are almost always described in patients who already suffer from very serious disease (38).

Thus far, there is no certainty about this matter with respect to Aspergillus; yet, occasionally, seemingly primary infections are observed. However, cases in which such a primary role is an established fact seem rare. Pre-existent disease has been found so frequently in the present series of cases that it is assumed that such secondary involvement is at least the most frequent, if not the only, form of aspergillosis. As this point is of great importance, especially for the treatment of the localized form, the cases have been recorded briefly in tables 1 and 4.

Secondary Aspergillus Infection or Saprophytism

It is believed that the question whether the fungus (in the cases in which it grows in cysts or cavities or manifests tuberculous or sarcoid origin) must be regarded as a pathogenic microorganism or as a saprophyte cannot be answered with certainty (figures 6–8). One argument in favor of saprophytism is the absence of any inflammatory reaction in the great majority of cases. But, by the same token, this reaction is not present in the definitely pathogenic cryptococcosis. Saprophytism is also supported by the

TABLE 3

CULTURE OF ASPERGILLUS FUMIGATUS (AND YEASTS) IN NORMAL SUBJECTS AND PATIENTS WITH PULMONARY DISEASES

(June–December, 1958)

Patients with Pulmonary Diseases	Type of Material	Number of Specimens (Number of Patients)	Temperature of Growth*	*Aspergillus fumigatus*			Yeasts	
				Positive Patients / Total Patients	Positive Specimen / Total Specimen	Positive Cultures / Total Cultures	Positive Patients / Total Patients	Positive Cultures / Total Cultures
Normals (students)	Throat swab	44 (44)	20–25	0/44	0/44	0/176	11/44	24/176
Miscellaneous patients†	Throat swab; mouth rinsing	191 (124)	20–25 20–37	2/124	2/191	2/754	86/124	292/754
Patients with pulmonary tuberculosis	Throat swab; mouth rinsing	86 (38)	20–25 20–37	0/38	0/86	0/344	29/38	134/344
Total control cultures Total mouth and throat	Throat swab; mouth rinsing	321 (206)	20–25 20–37	2/206	2/320	2/1274‡	128/206	450/1274
Sputa of patients§ with miscellaneous pulmonary diseases	Sputum‖ (washed)	138 (45)	20–25 20–37	5/45	13/138	14/552	13/45	37/552
Sputa of patients with pulmonary tuberculosis¶	Sputum (washed)‖	172 (28)	20–25 20–37	5/28	6/172	8/688	11/28	40/688
Total of sputa in lung diseases	Sputum (washed)‖	310 (73)	20–25 20–37	10/73	19/310	22/1270**	24/73	77/1240††

* Not all specimens were cultured at the same temperature. At first, cultured at 20–25°C.; later at 20–37°C. As far as could be established, there were no differences in the results.

† Approximately 50 per cent of the patients had nontuberculous pulmonary disease: asthma, bronchitis, bronchogenic carcinoma. The number of male and female patients was approximately the same.

‡ In one of the 2 patients the possibility of a pulmonary focus containing Aspergillus should be considered (tuberculous cavity). In the second one, there was an old tuberculous process (tuberculous spondilytis) but no pulmonary lesions.

§ A number of these had very extensive disease (emphysema, bronchiectasis, sarcoidosis).

‖ All specimens were cultured on Sabouraud agar and on malt agar at 20° and 25°C. or at 20° and 37°C.

¶ Partly with very extensive disease; a portion of the sputum was investigated particularly for this reason. The patients who have been considered cases of aspergillosis are not included. In these cases there are always a number of positive cultures.

** The positive cultures in the 22 cases were not included. In these cases large numbers of cultures were always positive.

†† The much lower results of positive yeast cultures in sputum are explained by the washing of the sputum, which makes the chance of growing, contaminating mouth flora much lower than when not washed or as the result of throat and mouth rinsing. In these cases usually only a few colonies are grown from the "washed" sputum.

fact that there is usually no production of sputum unless there are concomitant bacterial infections (rare with aspergilloma) or unless asthmatic symptoms exist.

In 34 cases, fairly good information (37, 38) was obtained concerning bacterial infection:

In 8 cases *Hemophilus influenzae* was repeatedly found, probably as a part of the chronic bronchitis which was diagnosed in these cases. In 15 cases a bacterial infection could be excluded with reasonable certainty. In 11 other cases, this was not possible. In the other 17 of the 51 cases, no satisfactory information was available.

Absence of pathogenic power is suggested because the process often remains stationary for years and usually the changes on the roentgenograms may as well be attributed to an intermittent evacuation of the cavitary process; this is especially manifest in the isolated focus. The existence of other cysts in the same or in the contralateral lung without any signs of fungous growth also argues against infection even under

TABLE 4
TYPE OF DISEASE IN WHICH ASPERGILLUS GROWTH WAS DEMONSTRATED

	Number of Cases	Primary Lesion
Aspergilloma		
Isolated primary	4	36, 37, 15?, 24
Isolated in other processes	6 (7)	Tuberculosis, 7?, 2?, (16?)
		Bronchitis (bronchiectasis) 1, 14, 41, 49
Aspergillus growth in processes of known etiology, sometimes with typical crescent:		
Tuberculosis	10 (12)	11, 19, 20, 22, 28, 30, 40, (41), 48, 51, 32, (33)
Bronchogenic carcinoma	1	10
Diffuse bronchiectasis	3	9, 13, 44
Diffuse bronchitis	4 (5)	16, 18, 27, 40, 42
Sarcoidosis	4	5, 6, 23, 38
Bilateral roentgenographic changes	4	3, 4, 46, 21
Aspergillus growth in bronchial stump after operation	3	Resection for pulmonary tuberculosis 12, 47, 17
Aspergillus growth in empyema	4 (5)	Resection for pulmonary tuberculosis 25, 26, 33
		Resection for mammacarcinoma, 50
		Sarcoidosis, spontaneous pneumothorax (6)
Generalized (septic meningitic) process	1 (2)	"Acute infection" 31; primary aspergillosis
		Meningeal metastasis in cases of bronchogenic carcinoma
Generalized diseases	3	Pancytopenia, 35
		M. Bechterew, 34, 45
Unknown	4	8, 29, 43, 39
Primary sensitization	0	

The cases in parentheses have also been calculated in another group.

favorable conditions. Another argument is that, in birds, the air bladders are sometimes filled with Aspergillus. Although such infection does not always lead to disease, a pathogenic (even fatal) process sometimes occurs and can be produced experimentally.

The fact that so far no "delayed type" of allergic reaction has been described might be used against the hypothesis of infection; although growth in the tissues seems to occur, no invasion or defense reaction normally takes place (there is a recent exception (49)). The same is true for the absence of antibodies, which have not been demonstrated so far.

Arguments in favor of pathogenicity of the microorganism are: the hemoptyses which occur in many cases; the occurrence of disseminations (case *No. 9*); and the presence of empyema.

With empyema, the pathogenicity does not seem to be very great as it usually is transient and occurs after resection or spontaneous pneumothorax (26, 50). The events in case *No. 6* might be explained as an expression of virulence. A similar explanation is possible for the slight pathologic-anatomic lesions that have been ascribed to the presence and growth of the fungus (51).

The Influence of Previous Use of Antimicrobial Drugs on the Pathogenesis of Aspergillus Infection

Only a few facts are established with respect to the problem of the influence of previous antimicrobial therapy on the occurrence of aspergillosis. It has been shown that, due to the suppression of the bacterial flora, more food became available for the fungi. Presumably, this would promote their growth and possibly their pathogenicity at sites where both bacteria and fungi had been present before (42). Neither the clinical experiences nor the experiments have so far made acceptable the development of serious Aspergillus infections in cases without a preexistent, very serious—often fatal—disease. Under these circumstances, it is correct, however, to contend that in cases in which antimicrobial drugs prevent the development of complicating fatal bacterial complications, growth of fungi may eventually become the direct cause of death (Case *No. 9*).

Sensitization

Sensitization against Aspergillus is by no means rare. This may be explained adequately by the frequent presence of several species of

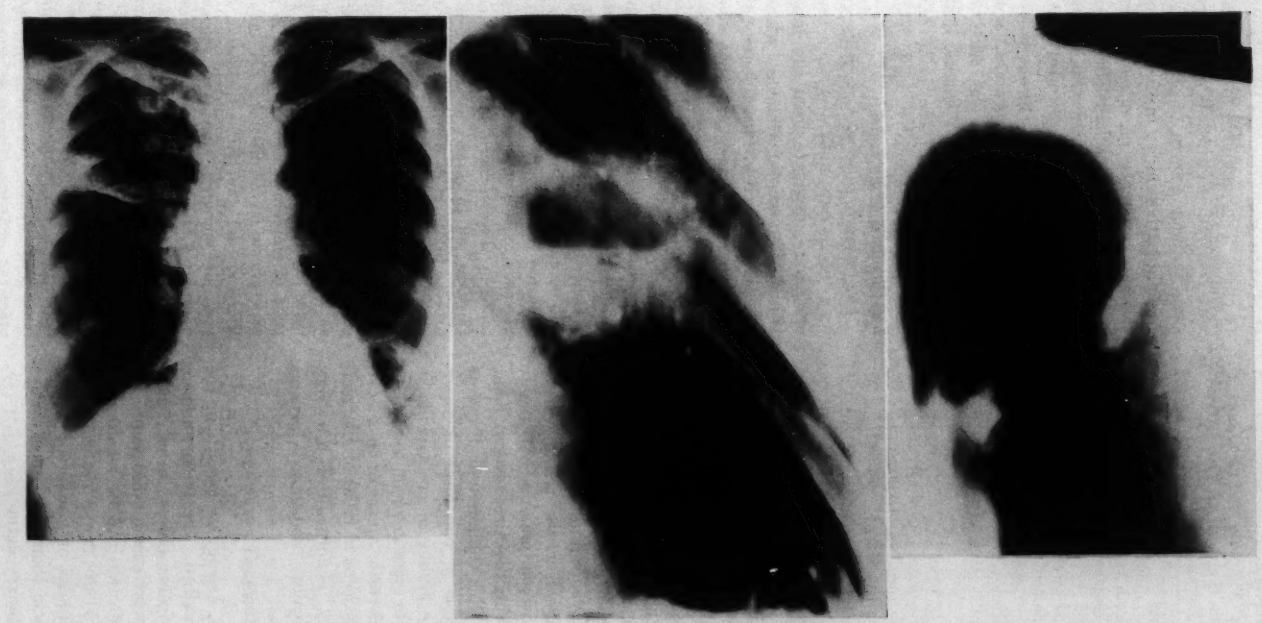

FIG. 6 (Left). Growth of *Aspergillus fumigatus* in a lobe with bronchiectasis (and possible arrested tuberculosis) (resection).
FIG. 7 (Center). Aspergillus growth in an infected area (pneumococcus) in an old arrested tuberculous process (resection).
FIG. 8. (Right). Aspergillus growth in an ectatic bronchus. Changing picture.

TABLE 5

IMMEDIATE TYPE OF ALLERGY IN 12 CASES IN WHICH ASPERGILLUS GROWTH IN THE LUNGS WAS ESTABLISHED

Case	Miscellaneous Allergens	Fungi	*Aspergillus fumigatus*
1	−	−	−
2	++	+	−
3	++	−	−
4	−	+	+
5	+	−	−
6	−	−	−
7	++	+±	+
8	±	−	−
9	+++	++	++±
10	−	+±	+
11	+	+	+
12	−	−	−

Interpretation of immediate type test, as mentioned by Ten Cate (52).

Aspergillus in the air (39). Whether this sensitization of the immediate type is also caused by fungous growth in the air passages is not very probable for reasons of analogy (tuberculosis, histoplasmosis, coccidioidomycosis). Nevertheless, it is not inconceivable. In patients in the present series in whom allergic responses were studied, the results are shown in table 5. It is not known with certainty how the result will be when (pre-existent or non-pre-existent) allergy concurs with growth in the air passages. Some investigators believe this combination of events forms the pathogenesis of one form of aspergillosis (17, 29). The finding of eosinophilia in the peripheral blood in cases in which the fungus is present in bronchiectatic areas, or in a cyst, forms in itself no argument in favor of allergization, for pulmonary abnormalities are very common in allergically predisposed persons (40, 53–55).

SUMMARY

Fifty-one cases of Aspergillus growth in the human lung are described. The microorganism was *Aspergillus fumigatus* (Fres) in all cases. In 44 cases a manifest pre-existent disease process was present. The infection can be regarded as local in 13 cases; in 15 cases it was localized in an extensive bilateral process of a different origin. The fungous growth was, therefore, almost always of a presumably secondary nature.

As a rule, the primary, secondary, and the local as well as the disseminated Aspergillus growth showed in many respects the character of saprophytism. The prognosis for empyema combined with Aspergillus growth is not different from the same without growth of *Aspergillus fumigatus*. A slight pathogenicity of the microorganism and the rare existence of primary local or septic processes are not excluded, however. Especially in the case of hemoptysis, the role of the fungus seems to be undeniable.

It is believed that terms like "Aspergillus sepsis," "Aspergillus infection," and "aspergillome bronchiectasiant" at least overestimate the significance of the fungus, if they are not entirely incorrect. These ideas have practical consequences, especially when operation of a local focus is being considered.

Operation in cases of Aspergillus growth in the lung (56) is only indicated when the complaints are severe, originate from the fungous growth (which is exceptional), and when the other affections, which are usually present (and their functional sequelae) do not contraindicate operation.

SUMARIO

Proliferación del Aspergilo en el Pulmón Humano: Aspergiloma y Aspergilosis

Descríbense 51 casos de proliferación del aspergilo en el pulmón humano. En todos los casos, el microbio fué el *Aspergillus fumigatus* (Fres.) En 44 casos existía un proceso manifiesto (preexistente). Cabe considerar la infección como local en 13 casos; en 15 estaba localizada en un extenso proceso bilateral de distinto origen. La proliferación fungosa era, pues, casi siempre de naturaleza presuntamente secundaria.

Por regla general, tanto la proliferación aspergilosa primaria (?) como la secundaria y la local así como la diseminada revelaban en muchos sentidos la naturaleza del saprofitismo. El pronóstico para el empiema combinado con la proliferación aspergilosa no es distinto del mismo sin proliferación del *Aspergillus fumigatus*. No se excluyen, sin embargo, una leve patogenicidad del microbio y la rara existencia de procesos primarios locales o sépticos. Sobre todo, tratándose de hemoptisis, el papel del hongo parece innegable.

Parece que términos tales como "septicemia aspergilosa," "infección aspergilosa" y "aspergillome bronchiectasiant" a lo menos exageran la importancia del hongo, si no son absolutamente inexactos. Estas ideas tienen consecuencias prácticas, máxime cuando se considera la operación de un foco local.

La operación de los casos de proliferación asper-

gilosa en el pulmón (54) está indicada únicamente cuando los síntomas son graves y proceden de la proliferación fungosa (lo cual es excepcional) y cuando las otras infecciones (que se hallan por consiguiente casi siempre presentes) y sus secuelas funcionales no contraindican la intervención.

Resume

Développement d'Aspergillus dans le poumon humain: Aspergillome et Aspergillose

Cinquante et un cas de développement d'Aspergillus dans le poumon humain sont décrits par les auteurs. Dans tous les cas, le micro-organisme était *Aspergillus fumigatus* (Fres.). Dans 44 cas, il y avait un processus préexistent manifeste. L'infection peut être considérée comme locale dans 13 cas; dans 15 cas, on la trouva dans un processus extensif bilatéral d'une origine différente. On présuma donc que le développement d'Aspergillus fut presque toujours de nature secondaire.

En règle générale, le développement d'Aspergillus, primaire et secondaire, et aussi bien locale que disséminé, montra de plusieurs façons, le caractère de saprophytisme.Le pronostic de l'empyème associé au développement d'Aspergillus, n'est pas différent de celui de l'empyème sans développement d'*Aspergillus fumigatus*. Un léger pouvoir pathogène du microorganisme et la rare existence de processus primaire local ou septique ne sont pas exclus cependant. Le rôle de l' Aspergillus semble être indéniable spécialement dans les cas d'hémoptysie.

On croit que les termes "septicémies à Aspergillus", "infection à Aspergillus", et "aspergillome bronchiectasique" exagèrent pour le moins la signification de l'Aspergillus, s'ils ne sont pas entièrement incorrects. Ces idées ont des conséquences pratiques, surtout quand on considère une opération pour un foyer localisé.

L'opération dans les cas de développement d'Aspergillus dans le poumon (54) est indiquée seulement quand les malades se plaignent d'une façon très accusée, lorsque la cause en est le développement d'Aspergillus(ce qui est exceptionnel), et quand les autres infections qui sont donc presque toujours présentes (et leurs séquelles fonctionnelles) ne contr'indiquent pas l'opération.

REFERENCES

(1) Dieulafoy, G., Chantemesse, A., and Widal, G. F. I.: Une pseudo-tuberculose mycosique, Congrès de Berlin, 1889.

(2) Renon, L.: *a*. Recherches cliniques et expérimentales sur la pseudo-tuberculose aspergillaire, Thèse de Paris 1893, p. 89. *b*. Etude sur l'aspergillose chez les animaux et chez l'homme, C. R. Soc Biol (Par), 1895–1896.

(3) Dieulafoy, G.: Manuel de pathologie Médicale, vol. 1, Masson et Cie., Paris, 1920.

(4) Langeron, M.: Précis de mycologie, Masson et Cie., Paris, 1945.

(5) Monod, O., Pesle, G., and Segrétain, G.: L'aspergillome bronchiectasiant, Presse Méd, 1951, *59*, 1557.

(6) Monod, O., and Lo, J.: A propos des aspergillomes bronchiectasiants, J Franc Méd Chir Thor, 1957, *11*, 257.

(7) Monod, O., Pesle, G., and Meyer, A.: L'aspergillome bronchiectasiant, Sem Hop Par, 1957, *33*, 3588.

(8) Pesle, G. D.: Evolution de l'aspergillome bronchiectasiant, Presse Méd, 1956, *68*, 1563.

(9) Bariety M. Poulet, J., Monod, O., and de Brun, J.: Aspergillose aigue purement pulmonaire, à forme de cancer bronchique, Bull Soc Med Hop Par, 1957, *14–15*, 397.

(10) Enjalbert, L., Segrétain, G., Eschapasse, H., Moreau, G., and Bourdin, M.: Deux cas d'aspergillose pulmonaire: Etude anatomo-pathologique, Sem Hop Par, 1957, *33*, 830.

(11) Legèse Bernard, M., Galy, P., Touraine, R.: Le mégamycétome pulmonaire ou aspergillome intracavitaire, J. Franc Med Chir Thor, 1953, *7*, 648.

(12) Martin-Lalande, J., and Lo, J.: Aspergillome bronchiectasiant associé à une tuberculose pulmonaire active: Résultats favorables d'un traitement médical antifungique, J Franc Méd Chir Thor, 1957, *11*, 77.

(13) Meyer, A., Monod, O., Pesle, G., Roy, L., Zivy, P., and Kuentz, J.: L'aspergillome bronchique, Bull Soc Med Hop Paris, 1956, *19–20*, 554.

(14) Quillec, P.: A propos d'un cas d'aspergillomes bilatéraux secondaires, J Franc Méd Chir Thor, 1958, *12*, 228.

(15) Tapie, J., Monnier, J., Le Fallec, Y., and Delande, A.: Aspergillose bronchopulmonaire avec alternances de bulles de condensations parenchymateuses, J Franc Méd Chir Thor, 1958, *12*, 130.

(16) Triglianos, A.: Quelques remarques bronchoscopiques sur les mycoses bronchopulmonaires, Poumon, 1954, *10*, 759.

(17) Hinson, K., Moon, A., and Plummer, N.: Broncho-pulmonary aspergillosis, Thorax, 1952, *7*, 317.

(18) Blanco Manuel, C.: Las micosis bronquiales en los asthmaticos, Rec Asoc Med Arg, 1939, *53*, 1105.

(19) Brunner, A.: Das sogenannte Aspergillom, Schweiz Med Wschr, 1958, *88*, 559.

(20) Owen, R.: Proc Zoöl Soc, London, 1832, p. 141.

(21) Hinshaw, H. and Garland, L.: Diseases of the Chest, W. B. Saunders Co., Philadelphia, 1956.

(22) RUBIN, E. H.: Diseases of the Chest, Emphasizing X-Ray Diagnosis, W. B. Saunders Co., Philadelphia, and London, 1947.

(23) CONANT, N. F.: Manual of Clinical Mycology, W. B. Saunders Co., Philadelphia, 1954.

(24) RUBINSTEIN, T: Micosis Broncapulmonares, Editorial Beta, Buenos Aires, 1954.

(25) PEUTZ, J. L. A.: Primaire aspergillose der longen, Ned T Geneesk, 1932, *76*, 446.

(26) BRONKHORST, W.: Dutch Association for Pulmonary Diseases and Tuberculosis, Meeting at Utrecht, 1956.

(27) KRAAN, J. K., AND ORIE, N. G. M.: Over schimmelziekte in de long, Ned T Geneesk, 1949, *93*, 530.

(28) VERBEKE, R.: Het aspergilloom van de long, Belg T Geneesk, 1953, *16*, 723.

(29) V. D. WERFF, P. J.: Pulmonary mycosis with and without asthma: The therapie of bronchial asthma, Proceedings of Round Table Friendship Meeting, Utrecht, May, 1955, H. E. Stenfert Kroese, N. V., Leiden, 1956, p. 317.

(30) HERS, J. F. PH., CORMANE, R. H., AND LAMERS, J. J. H.: Broncho-pulmonary aspergillosis, Thorax (in press).

(31) LOHMAN, A. J. M.: Bronchomycosis, Ned. T Geneesk, 1941, *85*, 3240.

(32) HINSON, K., MOON, A., AND PLUMMER, N.: Broncho-pulmonary aspergillosis, Thorax, 1952, *7*, 317.

(33) DEVÉ, F.: Une nouvelle forme anatomo-radiologique de mycose pulmonaire primitive: Le mégamycétome intra-bronchectasique, Arch Med Chir App Resp, 1938, *13*, 337.

(34) SAYER, R. R., AND MERRIWETHER, R.: Amer J. Roentgenol, 1932, *27*, 337.

(35) OLMER, J., AND PAYAN, H. C. S.: Mycose à forme cérébrale après antibiotherapie, Presse Méd, 1957, *65*, 1717.

(36) THOM, C., AND RAPER, K.: A Manual of the Aspergilli, Williams & Wilkins Co., Baltimore, 1945

(37) MULDER, J.: Bacteriology of bronchitis, Proc Roy Soc Med, 1957, *49*, 773.

(38) ORIE, N. G. M.: Candida (Monilia) infection of the respiratory tract, Dis Chest, 1952, *22*, 107.

(39) V.D. WERFF, P. J.: Mould Fungi and Bronchial Asthma. A Mycological Clinical Study, H. E. Stenfert Kroese, N. V., Leiden, 1958.

(40) V.D. PLAS, M. C.: Studie over behandeling van Haemophilus bronchitis met antibacteriele stoffen, Thesis, Leiden, 1951.

(41) ORIE, N. G. M.: Over het voorkomen en de betekenis van gisten in de luchtwegen, Thesis, Utrecht, 1946.

(42) CORMANE, R. H.: Candida albicans en therapie met antibiotica, Thesis, Leiden, 1958.

(43) BENHAM, R. W., AND HOPKINS, A. M.: Yeast-like fungi on the skin and in the intestines of normal subjects, Arch Derm, 1923, *28*, 1957.

(44) AINSWORTH, G. C., AND REIVELL, R. E.: The incidence of aspergillosis in wild birds, J Comp Path Ther, 1949, *59*, 253.

(45) LESBOUYRIES, G.: La Pathologie des Oiseaux, Paris, 1941.

(46) SEABURY, J. H., PEABODY, J. W., JR., AND SIBERMAN, M. J.: The usefulness of the Hotchkiss-Mc Manus stain for the diagnosis of deep mycosis, Dis Chest, 1954, *25*, 54.

(47) LITTMAN, M. L., AND ZIMMERMAN, L. E.: Cryptococcosis: Torulosis or European Blastomycosis, Grune & Stratton, New York and London, 1956.

(48) SIRVEN, R. H., BONFIGLIOLI, H., HOGMAN, D., LEMER, A., AND MACCHI, A.: Cryptococcus enfermedad de Hodgkin, Prensa Med Argent, 1955, *42*, 2192.

(49) PEPYS, J., RIDDLE, R. W., CITRON, K. M., CLAYTON, A. M., AND SHORT, E. I.: Clinical immunologic significance of *Aspergillus fumigatus* in the sputum, Amer Rev Resp Dis, 1959, *80*, 167.

(50) KISTERS, J. B.: Een merkwaardig longabces (schimmelinfectie), Ned T Geneesk, 1949, *93*, 2665.

(51) CORTEZ PIMENTAL, J. C.: New morphologic aspects of pulmonary aspergillomas: probable initial and residual states, Gaz Med Port, 1959, *12*, 333.

(52) TEN CATE, H. J.: Onderrock bij asthmapatiënten naar overgevoeligheid voor verstoven allergeen-entracten, Thesis, Groningen, 1954.

(53) WATSON, S. H., AND KIBLER, C. S.: Bronchiectasis, JAMA, 1938, *111*, 394.

(54) WARRINGA, R. J.: Over bronchiectasie, Thesis, Groningen, 1955.

(55) ISRAËLS, A. A.: Asthma bronchiale, etterige (bacteriele) bronchitis en het endocriene systeem, Thesis, Groningen, 1952.

(56) GRAVES, C. L., AND MILLMAN, M.: Lobectomy for fungous abcess of the lungs: Effect of penicillin, J Thor Cardiov Surg, 1951, *22*, 202.

EVALUATION OF THE TUBERCULOUS LUNG BY PULMONARY ANGIOCARDIOGRAPHY[1]

IRVING CHOFNAS

(Received for publication May 9, 1960)

Introduction

Pulmonary angiocardiography is a frequently used tool in clinical medicine today. It will clearly outline a suspected arteriovenous shunt of the lung. The extent of bullous emphysema can be delineated with increased clarity by demonstrating compression of the pulmonary vasculature. In the diagnosis of anomalous pulmonary vessels and congenital cardiac defects, this form of study has become routine. Angiocardiography is also most useful in separating the solid shadow due to heart or vessel from the shadow cast by a neoplasm.

Earlier reports by Steinbach and others (1–3) have demonstrated the obliteration of the pulmonary arterial blood supply to areas of lung involved by the tuberculous process. Most of this material antedates modern chemotherapy. The pathologic process involved in vascular obliteration within the tuberculous lung has also been pointed out earlier (4, 5). Bronchography, once considered inadvisable in the presence of tuberculosis, has with the advent of rapidly eliminated contrast media become an important part of the evaluation of patients.

Angiocardiography has not kept pace with bronchography in the study of patients afflicted with pulmonary tuberculosis. From the writer's experience in the 5 cases reported herein, it is believed that angiocardiography does have a place (although a limited one) in the study of tuberculous patients, along with bronchoscopy, bronchography, tomography, and studies of pulmonary function. The information obtained from this form of study, correlated with the bronchographic findings, is deemed worthy of presentation. All patients under discussion had had a period of antimicrobial therapy and had residual tuberculous disease when the angiocardiography was performed.

Methods

Angiocardiography: The contrast medium utilized for angiocardiography was 70 per cent sodium acetrizoate.

In the writer's experience, ease of injection of the product and clarity of visualization were impressive. Significant toxicity was not noted. Preliminary measures included a film of the chest, the injection of 1 ml. of the contrast medium to determine patient sensitivity, and finally measurement of the arm-to-tongue circulation time. The latter served as a gross test, indicating the need for alteration of basic timing. A "cutdown" was made over the antecubital vein and a catheter was inserted and attached through a three-way stopcock to a bottle of normal saline. The third orifice served as a portal for the injection of the contrast medium. With the apparatus in order the patient was placed in front of a stereo cassette with the timer set at two seconds. The subject took a deep breath slowly and held it at the end of inspiration. Just prior to the peak of this inspiration, 50 ml. of the radiopaque medium were injected rapidly and, when the plunger of the syringe reached the bottom of the barrel, the operator signaled that films be taken. The catheter could then be kept open with the intravenous saline while the films were reviewed wet. If the need for further study presented itself, the injection could be repeated only once. Part of the routine examination included a flat plate of the abdomen to demonstrate the coincidentally available outline of the genitourinary tract.

Bronchography: Bronchography was performed on each of the patients under study, using Dionisil® oily as contrast medium. Anesthesia of the nasopharynx and tracheobronchial tree was obtained with 2 per cent lidocaine (Xylocaine®). A rubber catheter inserted into the trachea served as a portal for filling the bronchial tree. Three milliliters of medium were employed for each of the six positions required to fill a lung. Each position was correlated with a portion of lung under study. The use of a tilt-table permitted the filling of the upper lobe. A fluoroscope was not used. It has been rare that information obtained from one of these procedures has been inadequate in the presence of good preoperative tracheobronchial toilet. The saving of time and physician irradiation should be noted.

[1] From Baylor University College of Medicine and the Veterans Administration Hospital, Houston, Texas.

Case Reports

Case 1 (figure 1). J. S., a 29-year-old Negro male, was admitted on June 16, 1956, to the Veterans Administration Hospital, Houston, Texas, in an acutely ill state. The patient appeared chronically, as well as acutely, ill. The temperature was 101.4°F. There was evidence of consolidation and contraction of the right lung on physical examination. Sputum cultures were positive for *Mycobacterium tuberculosis* in June and July, 1956, but all cultures thereafter were negative. On identifying the organism by direct microscopy, antimicrobial therapy, consisting of sodium PAS, 15 gm. per day, and isoniazid, 300 mg. per day, as well as streptomycin, 1 gm. daily initially (and later 1 gm. biweekly), was started and maintained until the time of discharge on September 6, 1957. The patient remained toxic throughout the month

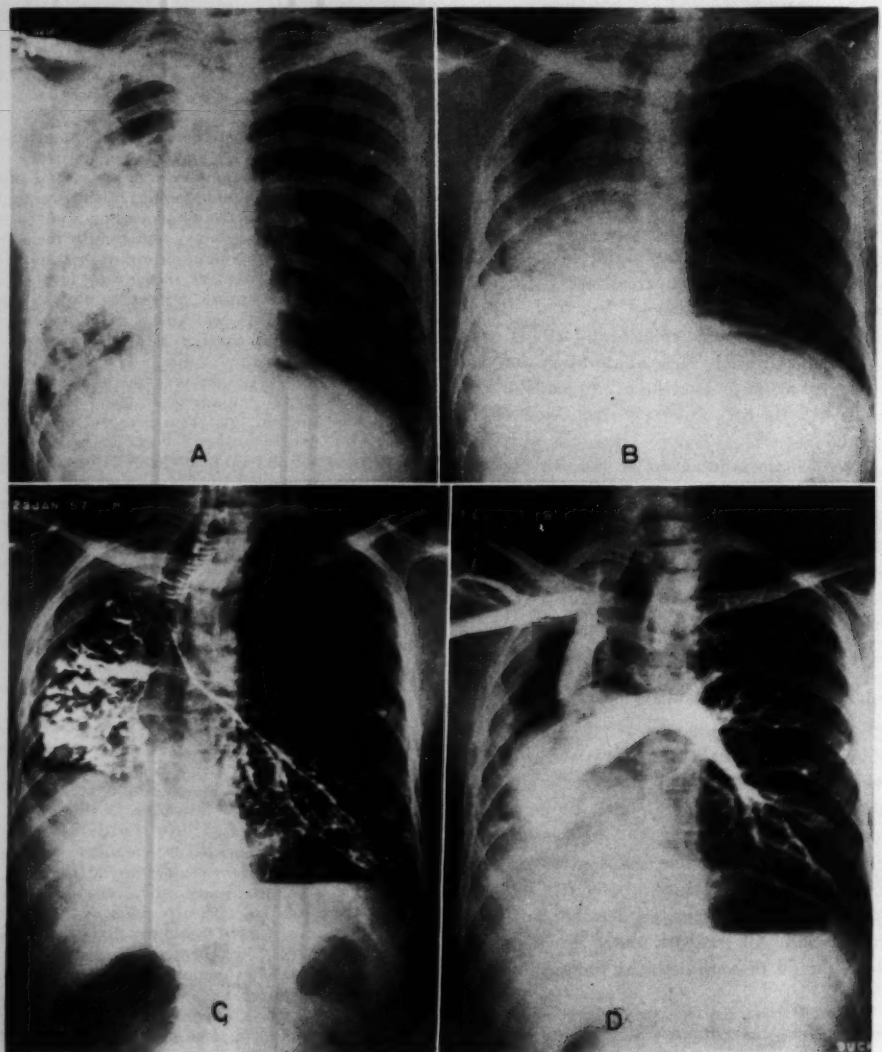

Fig. 1. *Case 1* (J. S.). *A*. Admission film, June, 1956. *B*. Film obtained in August, 1956. *C*. Bronchography, January, 1957. *D*. Pulmonary angiocardiography, February, 1957.

of July, 1956. Bronchography was performed on January 23, and angiocardiography on February 5, 1957. Basic pulmonary function studies demonstrated a vital capacity of 1,813 and a maximal breathing capacity of 21.3 liters per minute. Differential bronchospirometry demonstrated that 90 per cent of the vital capacity, 95 per cent of the oxygen consumption, and 94 per cent of the minute ventilation were performed by the left lung. The patient refused right pneumonectomy because of religious beliefs and was discharged with medical sanction September 6, 1957, with instructions to continue medication indefinitely.

Comment: The complete absence of pulmonary circulation to the right lung and the bronchiectatic distortion of its tracheobronchial tree should be noted in contrast to the condition on the left side. Angiocardiography and bronchography demonstrated graphically the absence of functioning lung tissue on the right. They further confirmed the impression that removal of this potential disease hazard should not deprive the patient of any functioning pulmonary tissue. This concept could be difficult to achieve by any other form of roentgenography.

Case 2 (figure 2). E. W., a 37-year-old white male, was transferred to the Veterans Administration Hospital, Houston, Texas, on March 20, 1957, for evaluation of the possibility of extirpative surgery. The patient's disease was first recognized in 1945. In 1948, he received pneumothorax on the left for a year. Efforts to institute right pneumothorax were unsuccessful about the same time. beginning in 1951, antimicrobial therapy, including streptomycin, PAS, and later isoniazid and viomycin in various combinations failed to reverse infectiousness and his bacilli were found to be drug resistant. The patient's complaints included dyspnea, wheezing, and production of about 150 ml. of purulent sputum per day. Included in the physical findings of note were limitation of respiratory excursion on the left and accentuation of the pulmonic second sound.

The laboratory study demonstrated a hemoglobin of 19.5 gm., hematocrit of 63 per cent, and sputum cultures positive for acid-fast bacilli which were resistant to the commonly used drugs. The patient's carbon dioxide content was 34 mEq. per liter. During the patient's relatively short stay in this hospital, bronchographic and angiocardiographic studies were included in the study. The electrocardiogram revealed a P-wave change compatible with cor pulmonale. Basic pulmonary function studies were interpreted as showing a marked combined ventilatory defect. Arterial oxygen saturation was shown to be undersaturated at rest, it dropped with exercise, but achieved 100 per cent saturation on breathing 100 per cent oxygen. It was generally agreed that surgery was not feasible, and the patient returned on May 3, 1957, to the hospital in which he was formerly a patient.

Comment: The bronchographic studies readily demonstrated the gross distortion of the patient's bronchial alveolar tree. They also outlined the large radiolucent residua of the patient's tuberculosis. Angiocardiography confirmed the impression of absence of blood from the pulmonary artery to areas destroyed by the tuberculous process. In addition to this, there was a great diminution of blood flow to the left lower lung field that had been diseased in the past and subjected to pneumothorax for a year. It is difficult to see how the latter abnormality could be demonstrated clinically by means other than the instillation of contrast medium into the vascular system.

Case 3 (figure 3). C. R., a 47-year-old white male, was admitted to the Veterans Administration Hospital, Houston, Texas, on September 15, 1956, for the first time. His illness began a month prior to admission and was marked by fever, weight loss, chilly sensations, and dry cough. There was a familial history of tuberculosis. Physical examination revealed an asthenic, chronically ill, white male, who looked older than his stated age. Bronchovesicular breath sounds, but no definite rales, could be heard in both upper lung fields. The pertinent laboratory data included cultures positive for acid-fast bacilli consistently through April 15, 1957. Thereafter, studies were negative for these organisms. Basic pulmonary function studies performed on October 10, 1957, revealed a vital capacity of 4,114 cc., a maximal breathing capacity of 79 liters per minute, and a one-second vital capacity of 65 per cent. Differential bronchospirometry on October 24 showed that the right side performed 63 per cent of the oxygen consumption, 58 per cent of the minute ventilation, and 57 per cent of the vital capacity. Isoniazid, 300 mg. per day, and pyrazinamide, 3 gm. per day, made up the initial therapy. On April 18, 1957, pyrazinamide was discontinued and streptomycin–PAS was substituted. The angiocardiographic studies were performed on May 2, 1957, and bronchography on June 14, 1957. On November 22, 1957, the left apical posterior segment was resected. Microscopic evaluation of the lung tissue was consistent with fibrous tissue. Culture of this tissue was negative for acid-fast bacilli. The patient was discharged on April 7, 1958, with instructions to continue drug therapy for a period of one year thereafter. He was last seen on October 12, 1959.

Comment: The demonstration of bronchiectatic residua and lack of pulmonary arterial blood flow to this involved area was again confirmed in this instance.

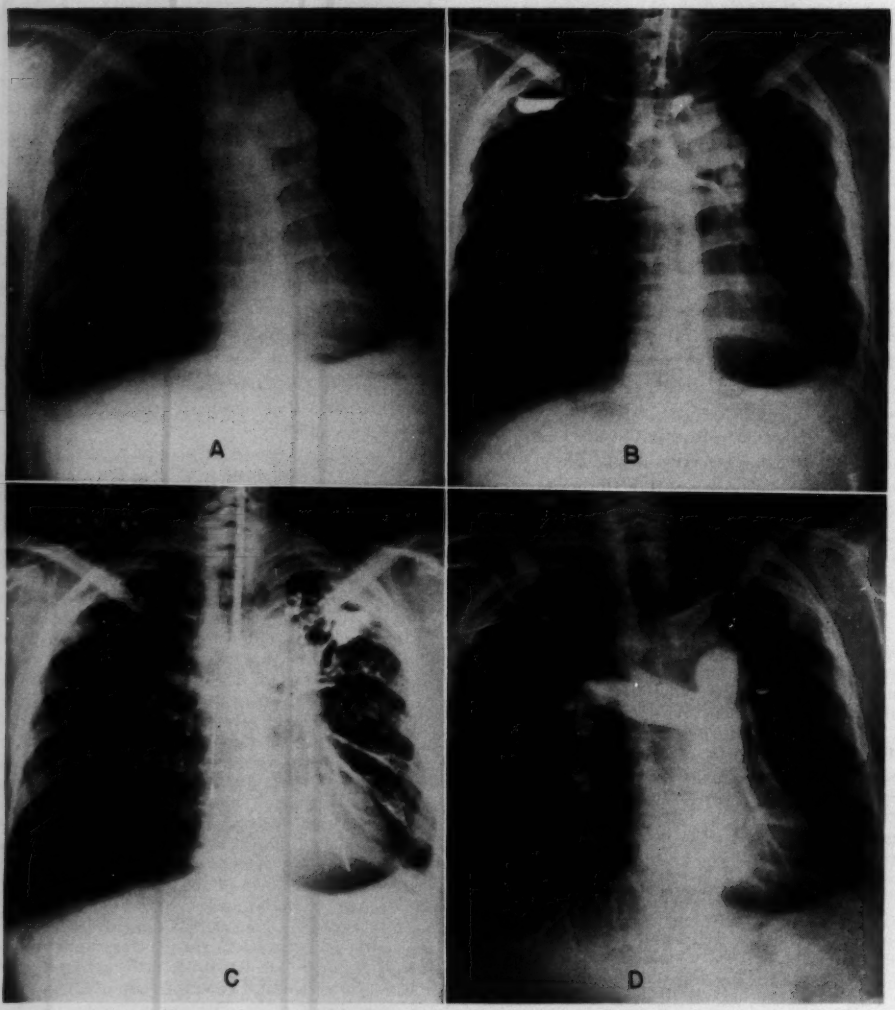

FIG. 2. *Case 2* (E. W.). *A*. Routine film obtained in April, 1957. *B*. Bronchogram, right, April, 1957. *C*. Bronchogram, left, March, 1957. *D*. Pulmonary angiocardiography, April, 1957.

Case 4 (figure 4). H. Y., a 26-year-old Negro male, was admitted to the Veterans Administration Hospital, Houston, Texas, on January 28, 1957, with a three-month history of cold, cough, and a 20-pound weight loss. The patient was a cook and had been obtaining chest films routinely at six-month intervals. Physical examination revealed many rales and increased breath sounds throughout both lung fields. Pertinent laboratory studies demonstrated sputum positive on microscopy and culture for acid-fast bacilli until March 25, 1957, and all specimens were negative thereafter. Shortly after admission to the hospital, therapy with isoniazid, 300 mg. per day, and pyrazinamide, 3 gm. per day, was begun. Because of hepatotoxicity, pyrazinamide was discontinued and streptomycin–PAS was substituted on March 20, 1957. The febrile state lasted approximately one month. Pulmonary angiocardiography was performed on May 27, 1957, and bronchography on June 1, 1957. Discharge to follow-up status took place on January 3, 1958, with instructions to continue on drugs.

Comment: Here is an example of bilateral reversible disease with an irreversible component

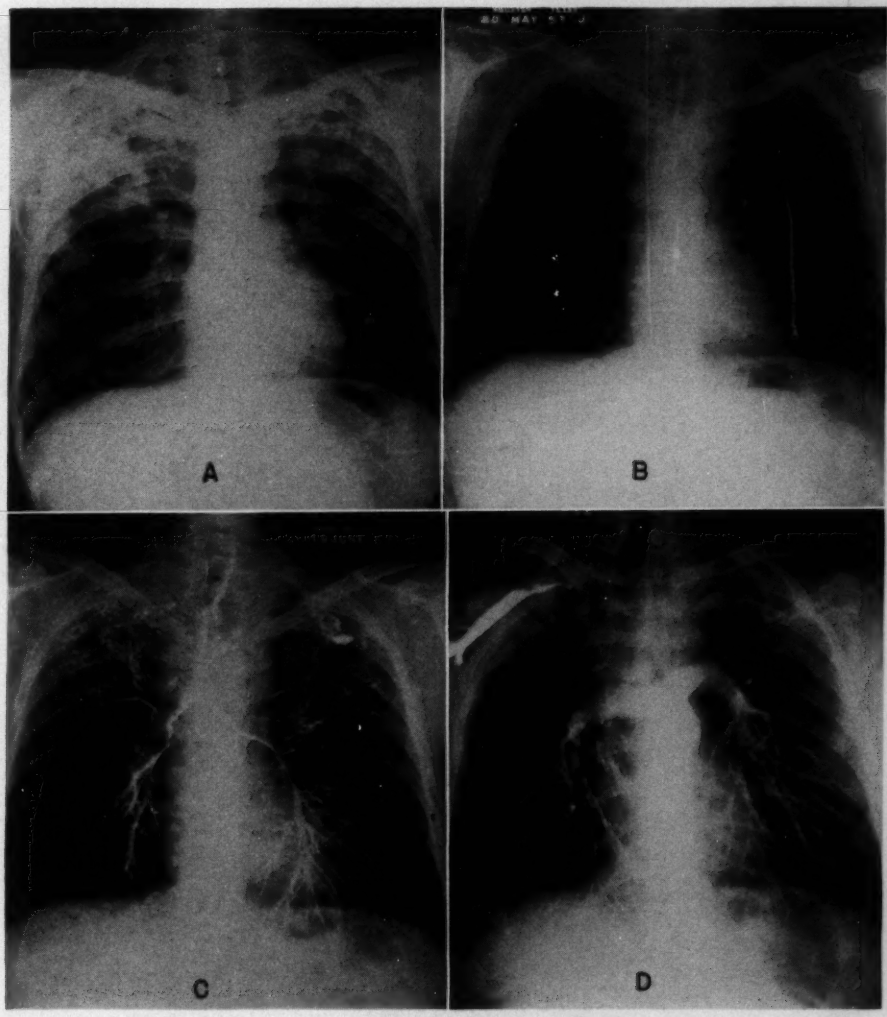

FIG. 3. *Case 3* (C. R.). *A*. Admission film, September, 1956. *B*. Film, May, 1957. *C*. Bronchography, June, 1957. *D*. Pulmonary angiocardiography, May, 1957.

limited to a small area in the right apex. This was confirmed by bronchographic and angiocardiographic evaluation. Here, one may gain the impression that these procedures could be of value in predicting reversibility of disease.

Case 5 (figure 5). F. W., a 51-year-old white male, was admitted to the Veterans Administration Hospital, Houston, Texas, on February 17, 1958, because of fistula in ano. He admitted to a 15-pound weight loss, night sweats, and aching chest pain for a period of six months. Physical examination revealed a chronically ill, undernourished, white male in no distress. Amphoric breath sounds, bronchial breathing, and posttussic rales were heard over the right upper lobe. A fresh granulating wound was noted in the rectal area. Pertinent laboratory studies revealed sputum cultures persistently positive for acid-fast bacilli until a right upper lobe lobectomy was performed on December 17, 1958. Thereafter, all sputum studies were negative. On admission the patient was placed on isoniazid, 600 mg. per day,

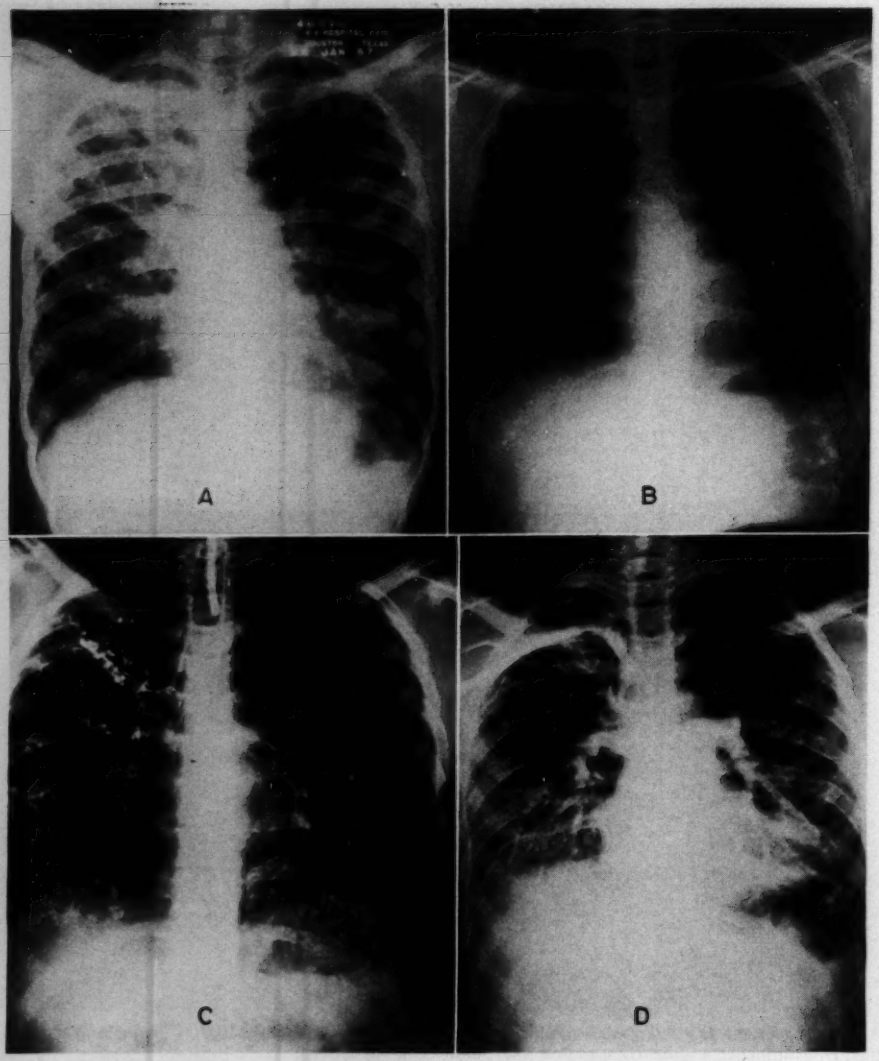

FIG. 4. *Case 4* (H. Y.). *A*. Admission film, January, 1957. *B*. Film, October, 1957. *C*. Bronchography, June, 1957. *D*. Pulmonary angiocardiography, May, 1957.

and sodium PAS, 15 gm. per day. In November, 1958, drug therapy was enhanced by the addition of streptomycin during a period in which surgery was to be performed. Bronchography was performed on December 2, 1958, and angiocardiography on December 4. The patient's discharge to follow-up status took place on May 15, 1959, with advice to continue drugs until December, 1959.

Comment: The bronchography in this case demonstrated an interesting anomalous finding consisting of separation of the right upper lobe bronchus so that the anterior segment of the bronchus and the one supplying the apical posterior segment originated independently from the right main-stem bronchus. Arterial blood

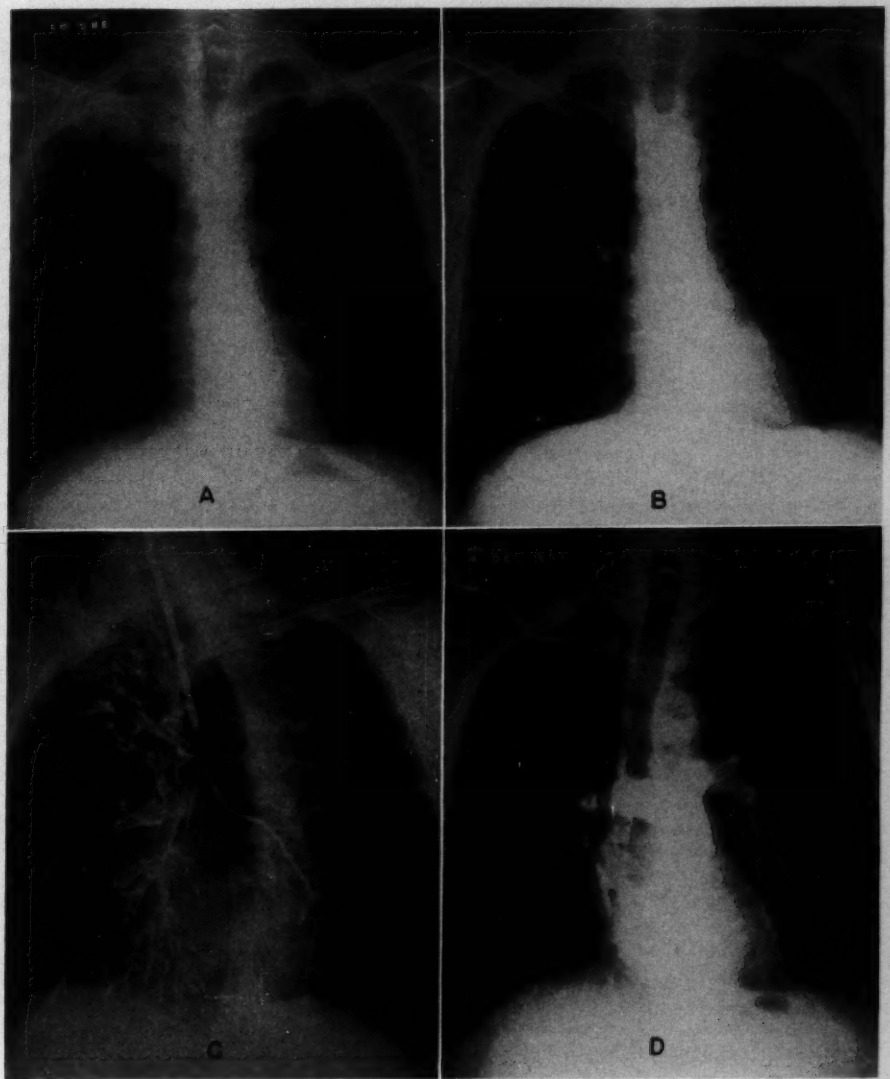

FIG. 5. *Case 5* (F. W.). *A*. Admission film, February, 1958. *B*. Film, December, 1957. *C*. Bronchography, December, 1958. *D*. Pulmonary angiocardiography, December, 1958.

flow was absent in the apical and posterior segments containing the bulk of the tuberculous residua.

DISCUSSION

Bronchography was almost a routine procedure in the present patient group under evaluation for surgery. The resulting delineation of segments or lobes involved by a disease marked by atelectasis and distortion of the tracheobronchial tree offered a more definite concept of the amount of lung that required surgical extirpation. Many times there are bronchiectatic changes in the lingula or apical segments of

lower lobes when the only residua evident on the plain film are localized to the upper third of the lung. Contrast media will frequently serve to outline the extent of a large multiloculated cavity with increased clarity. A suspected bronchopleural fistula can be clearly demonstrated by use of this procedure.

Pulmonary angiocardiography has been of limited value in the handling of patients. The obliteration of pulmonary arterial circulation in irreversible pulmonary tuberculosis is still the most striking finding. The most useful clinical application of this procedure is found when initial disease is advanced, resolution is marked, but bilateral residua, each with indication for surgery, remain. Functioning lung can be distinguished from nonfunctioning lung by combining pulmonary angiocardiography and bronchography. When the over-all pulmonary function is limited, the surgeon can utilize these procedures as a guide to the ultimate conservation of lung.

Lung tissue without pulmonary arterial blood is vascular when encountered at surgery. Studies demonstrating bronchial vascular dilatation and reverse flow from the bronchial arteries into the pulmonary artery following ligature of the latter vessel are compatible with the present findings (6, 7). The report of Alley and associates (8) of a case of chronic suppurative disease of the entire left lung with evidence of left ventricular hypertrophy on the electrocardiogram; increased right pulmonary arterial oxygen saturation in comparison to the right ventricle; marked increase of left heart over right heart output; nonfilling of the left pulmonary artery by pulmonary angiocardiography; and demonstration of dilated bronchial arteries with pulmonary arterial anastomosis of the excised left lung may well be the situation as it exists in the tuberculous residua in the present cases. The concept of a left-to-right shunt precipitates an indication for resective surgery that has received little consideration in the past. The possible sequela in the form of left ventricular hypertrophy has not been seen in the present series, but it does merit study in the future. At this point of the study it cannot be said whether there is or is not obliteration of the pulmonary arterial and venous blood supply within tuberculous residua. The bronchial arterial tree is accepted as the main source of blood supply to the areas under discussion. It is reasonable to conclude that removal of this tissue should not deprive the patient of functioning lung.

Equally important is an improved understanding of phenomena seen in pulmonary tuberculosis. Tuberculous patients very rarely demonstrate increased venous admixture of arterial blood. Bronchial arterial circulation as the sole source of blood will not lower oxygen saturation. The aneurysms of Rasmussen are known as a source of bright red exsanguination. The low-pressure, unoxygenated, pulmonary arterial circulation is not a likely point of origin of this hemoptysis. The peripheral high-pressure bronchial circulation is a far more likely culprit. Hemoptyses from present-day treated tuberculous residua and from the old bronchiectatic changes under thoracoplasty probably also have their point of origin in the bronchial circulation.

By delineating presence or absence of pulmonary arterial supply, angiocardiography can be of aid in distinguishing the reversible from the irreversible component early in the course of disease. This procedure should have diagnostic potential in differentiating tuberculous from other lesions.

The present cases demonstrate: striking loss of pulmonary circulation accompanying tuberculosis of the lung (*Cases 1–5*); increased clarity of the roentgenographic demonstration of existing circulation when there is massive loss of functioning lung (*Case 1*) and pulmonary hypertension (*Case 2*); presence of pulmonary circulation when there is reversible disease (*Case 3*); loss of pulmonary circulation in the presence of pulmonary hypertension in lung that had been subjected to pneumothorax for a year and a long period of functional immobilization (*Case 2*). There is a parallel relationship in the demarcation of destroyed areas of lung due to tuberculosis by bronchography and pulmonary angiocardiography.

Summary

Five cases of pulmonary tuberculosis are presented in which angiocardiographic and bronchographic procedures were performed. The details of each of these procedures are included. Angiocardiography has been simple to perform and has been accompanied by negligible morbidity. The data obtained from this procedure have been most informative, but its potential as a part of the practical clinical evaluation of the

tuberculous patient seems to be limited. On doing more of these studies, greater usefulness may be recognized. When pulmonary function must be carefully preserved in the face of extensive surgery, angiocardiography of the lung finds its greatest place in the care of the tuberculous patient. The phenomenon of a left-to-right shunt in tuberculous residual disease merits further study and evaluation.

Sumario

Justipreciación del Pulmón Tuberculoso por la Angiocardiografía Pulmonar

Preséntanse 5 casos de tuberculosis pulmonar en los que se ejecutaron procedimientos angiocardiográficos y broncográficos. Inclúyense los pormenores de cada uno de estos procedimientos. La angiocardiografía fué un estudio sencillo, yendo acompañada de una morbidad menospreciable. Los datos patológicos obtenidos a base clínica con este procedimiento han sido de lo más informativos. Parece ser limitado su potencial como parte de la justipreciación clínica práctica del tuberculoso. Al llevar a cabo más de estos estudios, tal vez se les encuentre mayor utilidad. Cuando, dada una cirugía extensa, hay que conservar meticulosamente la función pulmonar, la angiocardiografía del pulmón encuentra su puesto mayor en la asistencia del tuberculoso. El fenómeno de una desviación izquierda-a-derecha en los residuos tuberculosos es acreedor a mayor estudio y justipreciación.

Resume

Evaluation du poumon tuberculeux par angiocardiographie pulmonaire

L'auteur présente cinq cas de tuberculose pulmonaire dans lesquels on employa des procédés angiocardiographiques et bronchographiques. Les détails de chacun de ces procédés sont inclus dans le rapport. L'angiocardiographie a été une simple étude à obtenir et a été accompagnée d'une morbidité négligeable. Des données pathologiques, obtenues à partir des bases cliniques de ce procédé, ont apporté le plus de renseignements. Il semble que sa possibilité de constituer une partie de l'évaluation clinique pratique du malade tuberculeux est limitée. En faisant plus de ces études, on peut en reconnaître une utilité plus grande. Quand la fonction pulmonaire doit être préservée soigneusement en face d'une chirurgie extensive, l'angiocardiographie du poumon trouve sa place principale dans la conduite à tenir chez le malade tuberculeux. Le phenomène de "shunt," de gauche à droite, dans les séquelles tuberculeuses mérite une étude et une évaluation plus poussées.

Acknowledgment

The writer wishes to acknowledge his gratitude to Dr. Riley Foster of the Surgical Service for the performance of the pulmonary angiocardiograms, and to Mrs. Ella Mae Breckenridge of the Medical Illustration Service of this hospital for the illustrations. Dr. Daniel E. Jenkins, Professor of Medicine, Baylor University College of Medicine, offered advice and consultation in the preparation of this paper.

REFERENCES

(1) Steinberg, I., McCoy, H. I., and Dotter, C. T.: Angiocardiographic findings in artificial pneumothorax, Amer Rev Tuberc, 1950, *62*, 353.

(2) Steinberg, I., McCoy, H. I., and Dotter, C. T.: Angiocardiographic findings in pulmonary tuberculosis, Dis Chest, 1951, *19*, 510.

(3) Steinberg, I.: Angiocardiography in pulmonary disease, Amer J Surg, 1955, *89*, 215.

(4) Gale, G. L.: Vascular changes in the lungs in pulmonary tuberculosis, Amer Rev Tuberc, 1957, *75*, 410.

(5) Auerbach, O.: Anatomic changes in the lungs following thoracoplasty, J Thor Surg, 1941, *11*, 21.

(6) Hurwitz, A., Calabresi, M., Cooke, R. W., and Liebow, A. A.: An experimental study of the venous collateral circulation of the lung: I. Anatomical observations, Amer J Path, 1954, *30*, 1085.

(7) Hurwitz, A., Calabresi, M., Cooke, R. W., and Liebow, A. A.: An experimental study of the venous collateral circulation of the lung: II. Functional observations, J Thor Surg, 1954, *28*, 241.

(8) Alley, R. D., Stranahan, A., Kausel, H., Formel, P., and Van Mierop, L. H. S.: Demonstration of bronchial-pulmonary artery reverse flow in suppurative pulmonary disease, Clin Research, 1958, *1*, 41.

SHORT-TERM ANTIMICROBIAL THERAPY OF TUBERCULOUS MENINGITIS[1]

EDWIN L. KENDIG, JR., AND CHARLES D. BURCH

(Received for publication March 21, 1960)

Introduction

Tuberculous meningitis is the most serious form of tuberculosis. Mortality from this form o the disease was formerly 100 per cent, and it was not until the advent of streptomycin that the first victim survived (1). Addition of isoniazid to the therapeutic armamentarium has further improved the prognosis, but much remains to be accomplished.

With such a background, it seems appropriate that the Committee on Therapy of the American Trudeau (now Thoracic) Society has advised that treatment of tuberculous meningitis be continued for a minimum of eighteen months to two years (2).

In a previous publication, attention was called to a group of children with tuberculous meningitis, treated at the Medical College of Virginia Hospitals (3). Because of poor housing arrangements existing at that time, as well as various economic factors, these patients received early discharge from the hospital. This was done only after the advent of isoniazid, and follow-up observation by the Child Chest Clinic was anticipated. However, the patients came from many parts of the state, sometimes as far as 400 miles from Richmond; in many instances the expected therapeutic regimen did not materialize, and a relatively short course of antimicrobial therapy was effected. Since the progress of those patients so treated was unexpectedly satisfactory, duration of antimicrobial therapy for the majority of patients with tuberculous meningitis on the pediatric wards at the Medical College of Virginia Hospitals has been reduced to one year. Patients treated in this manner are herein reported, together with a follow-up report of those previously noted.

Materials and Methods

Criteria for diagnosis: Nineteen surviving patients received antimicrobial therapy for twelve months or less. In 9 cases, diagnosis was proved by demonstration of tubercle bacilli in culture of the cerebrospinal fluid. In the other 10, diagnosis was established by the typical clinical picture, cerebrospinal fluid findings compatible with tuberculous meningitis, and evidence of tuberculosis elsewhere. All of these children had positive reactions to the Mantoux test, 3 had miliary tuberculosis, one had tuberculous pneumonia, and 15 had primary pulmonary tuberculosis. Two of the latter had associated atelectasis, and one had tuberculosis of a superficial cervical lymph node (table 1).

Therapy: Antimicrobial therapy consisted of isoniazid, streptomycin, and para-aminosalicylic acid (PAS). The dosage of isoniazid varied from 6 to 20 mg. per kg. of body weight, with a maximal daily dose of 500 mg.; streptomycin was given in a dosage of 40 to 80 mg. per kg. of body weight, with a maximal daily dose of 1 gm.; and PAS, 200 mg. per kg. of body weight, with a maximal daily dose of 12 gm. All three drugs were used when therapy was instituted, but streptomycin (intramuscularly) was discontinued as soon after completion of a three-month course as activity of the disease process permitted. Only 6 patients received intrathecal streptomycin therapy. Corticosteroids were added to the therapeutic regimen in 16 cases, and the intrathecal administration of hydrocortisone was employed in 3 cases.

Observations

On the pediatric wards of the Medical College of Virginia Hospitals, 19 patients surviving tuberculous meningitis have received antimicrobial therapy, including isoniazid, for a period of twelve months or less. Of even greater significance is the fact that 11 patients received antimicrobial therapy for eight months or less, and the results were considered good in 8 of these patients. Two of the other 3 children seemed practically moribund during the early stages of treatment, but survived with diplegia (E. W.) and some mental retardation, and with moderate quadraplegia (J. M.), respectively. The other was semicomatose and had a history of illness of thirty days' duration. He has never completely regained consciousness.

Factors influencing outcome: It is well recognized that isoniazid has been a most effective antituberculous agent, and the writers' experience merely corroborates this general knowledge. Of

[1] From the Department of Pediatrics and the Child Chest Clinic, Medical College of Virginia, Richmond, Virginia.

38 children with tuberculous meningitis, whose treatment in the pediatric wards at the Medical College of Virginia included isoniazid, 28 (74 per cent) survived and there were 10 deaths. While it is encouraging to note the good results obtained in patients receiving a relatively short course of antimicrobial therapy, several factors must be considered in their evaluation.

Duration of symptoms before institution of therapy may not be readily measured because of the insidious onset of the disease. As far as can be determined, of those patients who received antimicrobial therapy for a period of twelve months or less and survived, the average duration of symptoms was eleven days. When those in this group whose result was considered good were tabulated, the average period in which symptoms were noted was also eleven days.

There was, then, no difference in duration of symptoms before institution of treatment in those survivors whose result was considered good and in those whose residual damage was enough to exclude them from the former group. Furthermore, there was no relapse in any of the surviving patients in either group.

The condition of the patient at the time of admission to the hospital seemed to be more indicative. Twelve of those 30 patients in the entire series who were comatose, semicomatose, or drowsy made good recoveries, 4 were considered to have had fair results, and in 5 the results were poor; 9 died. On the other hand, among those who were irritable, lethargic, or alert, 7 of the 8 recovered with little residual damage. However, difference in length of antimicrobial therapy appeared to exert no influence on the final outcome of patients in this series.

Eight patients had miliary tuberculosis, and 4 of these died. In 3 of the 4 survivors, the result was considered good, and only one of these received antimicrobial therapy for more than a twelve-month period.

The average age of the survivors, who received antimicrobial therapy for twelve months or less, was forty-one months. Eight of the 14 whose results were considered good were two years of age or younger.

Comment

In an earlier publication (3), report was made of a small group of patients with tuberculous meningitis who survived after a relatively short course of antimicrobial therapy. Since the results were unexpectedly good, the course of antimicrobial therapy for children with tuberculous meningitis treated at the Medical College of Virginia Hospitals was reduced to approximately twelve months. Indeed, it appears that this shortened course is not without precedent. Lorber (4) has suggested that antimicrobial therapy of tuberculous meningitis be carried out for a minimal period of six months. However, Fyfe (5) reported 5 patients treated less than six months; the disease in 3 of these relapsed, 2 patients died, and one had a further course of therapy because of roentgenographic changes in the chest indicating deterioration.

The patients whose course has been reported have fared exceedingly well. From the material at hand, it appears that antimicrobial therapy of twelve months' duration will be sufficient in a large number of cases. Indeed, while there were 5 relapses in patients at the Medical College of Virginia Hospitals treated without isoniazid, there has been no instance of relapse in the presently reported group, whether antimicrobial therapy was discontinued after a period of twelve months or less or continued for a longer period of time. There also appeared to be no deterioration of the patients' condition after the drugs were discontinued.

It is suggested, therefore, that many cases of tuberculous meningitis may be effectively managed by a twelve-month course of antimicrobial therapy, including isoniazid, although it must be emphasized that considerable caution should be exercised in choosing this shorter regimen.

Summary

Nineteen children, surviving tuberculous meningitis, received antimicrobial therapy for twelve months or less, and 11 of these were treated for eight months or less. The average duration of follow-up study was fifty-two months, with no instance of relapse. It is suggested that a twelve-month course of antimicrobial therapy, including isoniazid, may be effectively employed in many cases of tuberculous meningitis in children, although caution must be exercised in the decision to employ this shorter regimen.

Sumario

Antimicrobioterapia a Breve Plazo de la Meningitis Tuberculosa

Diecinueve niños, que sobrevivieron una meningitis tuberculosa, recibieron terapéutica anti-

TABLE 1

STATISTICS AS OF JANUARY 1, 1960

(Includes Hospital Admissions to July 1, 1958)

Patient	Age	Race	Sex	Duration of Symptoms	Condition at Time of Admission	Duration of Antimicrobial Therapy		Cerebrospinal Fluid Findings	Results	Other Tuberculosis Evidence	Duration of Follow-up Study
				days							*months*
G. G.	4 years	White	Male	14	Drowsy	PAS Streptomycin Isoniazid	−10 months 3 months 10 months	200 leukocytes Lymphs* 78% Protein 50 Sugar 25 Culture positive	Good	Positive OT Primary tuberculosis	39
H. W.	4 months	Negro	Male	6	Drowsy	PAS Streptomycin Isoniazid	10 days 10 days 10 days	Negative	Died	Positive OT Primary tuberculosis Autopsy: tuberculous meningitis	Died
C. G.	2½ years	Negro	Male	14	Semicomatose	PAS Streptomycin Isoniazid Streptomycin IT†	18 days 18 days 18 days 18 days	681 leukocytes Lymphs 63% Protein 600 Sugar 50 ‡	Died	Positive OT Primary tuberculosis	Died
V. W.	16 months	Negro	Female	14	Semicomatose	PAS Streptomycin Isoniazid	1 month 1 month 1 month	130 leukocytes Lymphs 73% Protein 200 Sugar 54	Died	Positive OT Autopsy: tuberculous; meningitis	Died
T. J.	6 years	Negro	Male	21	Acutely ill (alert)	PAS Streptomycin Isoniazid Streptomycin IT	8 months 8 months 8 months 40 injections	232 leukocytes Lymphs 30% Protein 20 Sugar 64	Died	Positive OT Miliary tuberculosis	Died

L. M.	11 months	Negro	Male	14	Comatose	PAS Strepto-mycin Isoniazid Strepto-mycin IT	12 months 12 months 12 months 40 injections	56 leukocytes Lymphs 33% Protein 70 Sugar 18	Poor	Positive OT Culture positive; gastric washings, primary tuberculosis	58
E. W.	2 years	Negro	Female	5	Drowsy	PAS Strepto-mycin Isoniazid	8 months 7 months 8 months	153 leukocytes Lymphs 86% Protein 200 Sugar 70 Culture positive	Fair	Positive OT Primary tuberculosis	63
T. H.	14 months	White	Male	11	Irritable	PAS Strepto-mycin Isoniazid	3 months 3 months 7 months	146 leukocytes Lymphs 83% Protein 120 Sugar 39 §	Good	Positive OT Tuberculous pneumonia	59
C. A.	5 years	White	Male	14	Comatose	PAS Strepto-mycin Isoniazid	5 months 5 months 10 months	396 leukocytes with 26% lymphs Protein 90 Sugar 38	Died	Positive OT Miliary tuberculosis (autopsy)	Died
R. M.	16 months	Negro	Male	28	Comatose	PAS Strepto-mycin Isoniazid	4 months 4 months 4 months	277 leukocytes with 98% lymphs Protein 90 Sugar 43 Culture positive	Died	Positive OT Miliary tuberculosis (autopsy)	Died
C. S.	5 years	Negro	Male	5	Alert	PAS Strepto-mycin Isoniazid Strepto-mycin IT	2 months 2 months 9 months 29 injections	68 leukocytes with 57% lymphs Protein 68 Sugar 40	Good	Positive OT Miliary tuberculosis	83

TABLE 1—CONTINUED

Patient	Age	Race	Sex	Duration of Symptoms	Condition at Time of Admission	Duration of Antimicrobial Therapy		Cerebrospinal Fluid Findings	Results	Other Tuberculosis Evidence	Duration of Follow-up Study
				days							*months*
G. T.	23 months	Negro	Male	7	Irritable	PAS Streptomycin Isoniazid Streptomycin IT	4 months 4 months 9 months 40 injections	818 leukocytes with 44% lymphs Protein 68 Sugar 57	Good	Positive OT Primary tuberculosis	83
M. J.	2 years	Negro	Female	28	Drowsy	PAS Streptomycin Isoniazid	5 weeks 6 months 6 months	107 leukocytes Lymphs 76% Protein 100 Sugar 50	Good	Positive OT Miliary tuberculosis	63
E. L.	4 years	Negro	Male	10	Semicomatose	PAS Streptomycin Isoniazid	7 months 5 months 11 months	521 leukocytes Lymphs 33% Protein 270 Sugar 22 Culture positive	Good	Positive OT Primary tuberculosis with atelectasis	54
J. C.	8 years	White	Male	7	Drowsy	PAS Streptomycin Isoniazid	4 months 4 months 6 months	232 leukocytes Lymphs 46% Protein 170 Sugar 32	Good	Positive OT Primary tuberculosis	71
E. B.	5 years	Negro	Male	28	Alert	PAS Streptomycin Isoniazid	6 months 21 months 21 months	370 leukocytes Lymphs 99% Protein 120 Sugar 41	Good	Positive OT Primary tuberculosis	62
L. G.	10 months	Negro	Male	5	Semicomatose	PAS Streptomycin Isoniazid Streptomycin IT	9 months 10 months 10 months 40 injections 2 weeks	125 leukocytes Lymphs 62% Protein 130 Sugar 41	Died	Positive OT Primary tuberculosis	Died

V. K.	2 years	Negro	Female	14	Comatose	PAS Strepto- mycin Isoniazid	5 months 5 months 8 months	393 leukocytes Lymphs 51% Protein 168 Sugar 66 ‖ Culture positive	Good	Positive OT Primary tuberculosis; atelectasis	55
N. B.	21 months	White	Male	6	Drowsy	PAS Strepto- mycin Isoniazid	3 months 3 months 2 years	198 leukocytes Lymphs 81% Protein 70 Sugar 36	Fair (deaf)	Positive OT Primary tuberculosis	71
M. M.	11 months	Negro	Male	30	Semi-comatose	PAS Strepto- mycin Isoniazid	3 months 3 months 8 months	706 leukocytes Lymphs 28% Protein 225 Sugar 25 Culture positive	Poor	Positive OT Miliary tuberculosis	42
S. S.	17 months	White	Female	9	Irritable	PAS Strepto- mycin Isoniazid	5 months 5 months 8 months	75 leukocytes Lymphs 80% Protein 40 Sugar 54 ¶	Good	Positive OT Primary tuberculosis; tuberculous adenitis	79
F. C.	7 years	White	Male	21	Semi-comatose	PAS Strepto- mycin Isoniazid	3 months 4 months 22 months	234 leukocytes Lymphs 92% Protein 70 Sugar 33	Fair	Positive OT Primary tuberculosis	63
P. B.	2 years	Negro	Female	9	Drowsy	PAS Strepto- mycin Isoniazid	4 days 4 days 4 days	197 leukocytes Lymphs 54% Protein 110 Sugar 12	Died	Autopsy: Tuberculous meningitis	Died
B. H.	28 months	Negro	Female	14	Comatose	PAS Strepto- mycin Isoniazid	6 days 6 days 6 days	25 leukocytes Lymphs 96% Protein 74 Sugar 56 **	Died	Autopsy: Tuberculous meningitis	Died

TABLE 1—CONTINUED

Patient	Age	Race	Sex	Duration of Symptoms	Condition at Time of Admission	Duration of Antimicrobial Therapy		Cerebrospinal Fluid Findings	Results	Other Tuberculosis Evidence	Duration of Follow-up Study
				days							*months*
C. O.	12 months	Negro	Male	3	Moribund	PAS Streptomycin Isoniazid	6 months 3 months 6 months	340 leukocytes Lymphs 92% Protein 168 Sugar 70 Culture positive ††	Good	Positive OT Primary tuberculosis	51
J. R.	12 years	Negro	Male	10	Lethargic	PAS Streptomycin Isoniazid	3 months 3 months 5 months	326 leukocytes Lymphs 76% Protein 126 Sugar 40	Good	Positive OT Primary tuberculosis	62
B. L.	29 months	White	Female	28	Comatose	PAS Streptomycin Isoniazid	5 months 3 months 16 months	227 leukocytes Lymphs 53% Protein 80 Sugar 45 Culture positive ‡‡	Good	Positive OT Primary tuberculosis	41
J. M.	9 years	White	Male	8	Semi-comatose	PAS Streptomycin Isoniazid	8 months 4 months 8 months	250 leukocytes Lymphs 93% Protein 200 Sugar 32 Culture positive	Fair	Positive OT Primary tuberculosis	34
B. B.	6 years	Negro	Male	11	Drowsy	PAS Streptomycin Isoniazid	4 months 4 months 29 months	105 leukocytes Lymphs 88% Protein 110 Sugar 33	Good	Positive OT Primary tuberculosis	63
C. K.	3 years	White	Female	21	Irritable	PAS Streptomycin Isoniazid	6 months 1 month 16 months§§	209 leukocytes Lymphs 77% Protein 120 Sugar 56	Good	Positive OT Miliary tuberculosis	19

R. B.	18 months	Negro	Male	3	Comatose	PAS Strepto-mycin Isoniazid	11 months 1 month 11 months	318 leukocytes Lymphs 60% Protein 120 Sugar 29 Culture positive	Poor	Positive OT	19
R. M.	4 years	Negro	Male	14	Drowsy	PAS Strepto-mycin Isoniazid	11 months 1 month 11 months	820 leukocytes Lymphs 90% Protein 300 Sugar 18 Culture positive	Good	Positive OT Primary tuberculosis	24
F. L. W.	3 years	Negro	Male	7	Semi-comatose	PAS Strepto-mycin Isoniazid	12 months 6 months 12 months	517 leukocytes Lymphs 74% Protein 200 Sugar 41 III	Poor (de-cerebrate)	Positive OT Primary tuberculosis; gastric culture positive	34
F. W.	10 months	Negro	Male	24	Comatose (hydro-cephalus)	PAS Strepto-mycin Isoniazid	12 months 5 months 18 months	No record; treated in another hospital for 4 months	Poor	Positive OT Primary tuberculosis	32
W. G.	4 years	Negro	Male	14	Drowsy	PAS Strepto-mycin Isoniazid	6 months 3 months 16 months	244 leukocytes Lymphs 76% Protein 125 Sugar 57	Good	Positive OT	31
C. K.	2 years	White	Female	Hospitalized elsewhere 6 weeks	Drowsy	PAS Strepto-mycin Isoniazid	7 months 3 months 7 months	170 leukocytes Lymphs 83% Protein 60 Sugar 35	Good	Positive OT Primary tuberculosis	21
P. B.	2 years	Negro	Female	7	Comatose	PAS Strepto-mycin Isoniazid	1 week 1 week 1 week	372 leukocytes Polys 89% Protein 600 Sugar 111 (after glucose)	Died	Positive OT Miliary tuberculosis; positive autopsy findings	Died

TABLE 1—CONCLUDED

Patient	Age	Race	Sex	Duration of Symptoms	Condition at Time of Admission	Duration of Antimicrobial Therapy		Cerebrospinal Fluid Findings	Results	Other Tuberculosis Evidence	Duration of Follow-up Study
				days							*months*
R. L.	2 years	White	Female	14	Drowsy	PAS	6 months	1,108 leukocytes	Good	Positive OT	18
						Strepto-mycin	4½ months	Lymphs 80%		Tuberculous pneumonia	
						Isoniazid	19 months	Protein 180			
								Sugar 37			

* Lymphocytes
† Intramuscularly
‡ Blood sugar, 146 mg. per 100 ml.
§ Blood sugar, 113 mg. per 100 ml.
‖ Blood sugar, 166 mg. per 100 ml.
¶ Blood sugar, 146 mg. per 100 ml.
** Blood sugar, 130 mg. per 100 ml.
†† Blood sugar, 250 mg. per 100 ml.
‡‡ Blood sugar, 133 mg. per 100 ml.
§§ Patient still receives isoniazid therapy.
‖‖ Blood sugar, 107 mg. per 100 ml.

microbiana durante doce meses o menos, y 11 de ellos fueron tratados durante ocho messes o menos. La duración media del estudio de observación subsiguiente fué de cincuenta y dos meses, sin ningún caso de recidiva. Sugiérese que, aunque hay que desplegar cautela, en muchos casos de meningitis tuberculosa en niños puede emplearse eficazmente una serie de doce meses de terapéutica antimicrobiana si se decide emplear este régimen más corto.

Resume

Thérapeutique antimicrobienne à court terme dans la méningite tuberculeuse

Dix-neuf enfants, ayant survécu à une méningite tuberculeuse, reçurent une thérapeutique antimicrobienne pendant douze mois ou moins, et 11 de ceux-ci furent soignés pendant huit mois ou moins. La durée moyenne d'étude pour suivre le cas fut de cinquante deux mois, sans cas de rechute. Ceci fait penser qu'une durée de douze mois de thérapeutique antimicrobienne, y compris l'isoniazide, peut être employée d'une façon efficace dans beaucoup de cas de méningite tuberculeuse chez les enfants, bien qu'il faille le faire avec précaution dans la cas où l'on décide d'employer ce mode de traitement plus court.

REFERENCES

(1) Cooke, R. E., Dunphy, D. L., and Blake, F. G.: Streptomycin in tuberculous meningitis: Report of its use in a one-year-old infant, Yale J Biol Med, 1946, *18*, 221.

(2) American Trudeau Society: Statement by Committee on Therapy concerning treatment of tuberculous meningitis, Amer Rev Tuberc, 1954, *70*, 746.

(3) Kendig, E. L., Jr., and Johnston, W. B.: Short-term antimicrobial treatment of tuberculous meningitis, New Engl J Med, 1948, *258*, 928.

(4) Lorber, J.: Current results in treatment of tuberculous meningitis and miliary tuberculosis, Brit Med J, 1956, *1*, 1009.

(5) Fyfe, W. M.: Treatment of tuberculous meningitis, Arch Dis Child, 1959, *34*, 334.

PULMONARY TUBERCULOSIS IN THE AGED[1]

J. ROBERT THOMPSON

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Introduction

That tuberculosis is a problem in elderly people is made evident by the fact that the average age of tuberculous patients in a sanatorium has increased over the years and, furthermore, that there has been a striking increase in the number of patients seventy years of age and older. Most of the reports in the past dealing with the aged have related to people more than sixty-five years of age. Medlar and associates (1) referred to patients in this category as "the disregarded seed-bed of the tubercle bacillus" and Myers (2) called attention to "tuberculosis lurking amongst the aged." Barber (3) considered this disease "a geriatric problem." The majority of the patients in this age group have gone through their productive years without any difficulty, only to develop clinical tuberculosis during their retiring or fading years.

In a review of the status of pulmonary tuberculosis in England and Wales from 1938 to 1956, Wilkins (4) stressed the following facts: the morbidity rates per 100,000 population rose from 50 to more than 80 for men, whereas for women they remained around 17. The mortality rates for men more than sixty-five years of age rose from 58 per 100,000 in 1938 to a peak of 81 in 1951. However, there was a steady decline in the mortality rates for women from 22 per 100,000 in 1938 to a low of 13. Several interesting studies have been carried out in reference to the tuberculin reaction of elderly people. Amazon (5) tested 619 persons more than sixty-five years of age and found that 22 per cent did not react to 0.1 mg. of Old Tuberculin (OT). Thirty-six per cent of the nonreactors showed roentgenographic evidence of tuberculous infection. In 1958, Beresford (6) tested 1,012 people in a comparable age group and found that a high percentage had negative tuberculin reactions. Of the nonreactors, 20 per cent showed roentgenographic evidence of previous infection. In testing a group of old people presumably free of active tuberculosis, Chesrow and Novak (7) found 81.5 per cent of reactors in the fifty- to sixty-nine-year age group, 74.2 per cent reactors in the seventy- to eighty-nine-year age group; in those patients more than ninety years of age, only 53.3 per cent reacted to 0.1 mg. of OT.

Method of Study

An analysis was made of all of the autopsies performed at the Municipal Tuberculosis Sanitarium during the ten-year period 1950 through 1959. There was a total of 801 patients, of whom 569 were men and 232 were women. The patients were grouped according to age in decades (figure 1). The chart shows that the preponderance of patients were in the third, fourth, fifth, and sixth decades at the beginning of the period; whereas, in the later years, the majority of the patients fell into the fifth, sixth, seventh, and eighth decades. As may be seen from the chart, the greatest number of deaths occurred in the sixth decade. In the eighth-decade group, there were 89 patients (69 men and 20 women). A breakdown of this group reveals that 39 patients were between the ages of seventy and seventy-four, 36 patients between the ages of seventy-five and seventy-nine, and 14 patients more than eighty years of age.

Observations

The year-by-year breakdown for men and women is shown in figure 2. A very marked increase may be seen in the number of cases to the highest total (22) in 1959. This figure represents approximately 20 per cent of the autopsies for that year. According to the histories given, the interval of time between the death of the patient and the onset of his disease was less than five years in 58 of the cases. The interval of time was greater than five years in 18 of the cases, and it was impossible to arrive at any given time interval in 13 cases. Positive bacteriology was obtained in 60 patients, 18 patients did not have any record of sputum positive for *M. tuberculosis* on microscopy or culture, and in 11 cases the bacteriologic findings were questionable. Examination of the lungs at the time of autopsy revealed that 44, or approximately one-half of the patients, had evidence of pulmonary tuberculosis with cavitation; the remaining 45 showed only fibrocaseous disease without gross evidence of cavitation.

[1] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

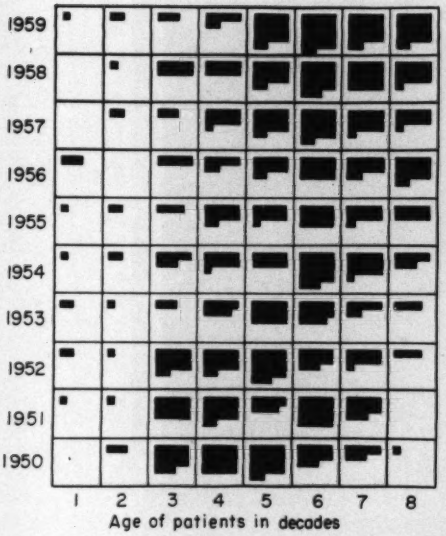

FIG. 1. Each small square represents one patient. Note the preponderance of patients in the fifth, sixth, seventh, and eighth decades in the latter part of the ten-year period as compared with the first part of the period when the majority fell into the third, fourth, and fifth decades.

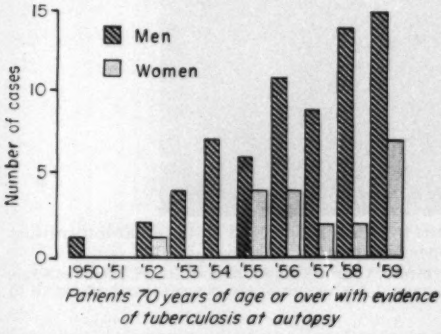

FIG. 2. A graphic illustration of the number of patients with pulmonary tuberculosis examined at autopsy over the last ten years. Note the marked increase over the past few years and the preponderance of men.

Diseases associated with pulmonary tuberculosis in this group of patients are listed in table 1. There were 15 pulmonary cancers and 18 extrapulmonary cancers. In addition, 53 patients showed some degree of nephrosclerosis and 39 showed chronic reactive hepatitis represented by various degrees of periportal fibrosis and infiltration with chronic inflammatory cells, mostly lymphocytes.

TABLE 1

DISEASES ASSOCIATED WITH PULMONARY TUBERCULOSIS IN 89 PATIENTS MORE THAN 70 YEARS OF AGE

	Male	Female	Total
Pulmonary cancer	12	3	15
Extrapulmonary cancer	14	4	18
Benign nephrosclerosis	45	8	53
Chronic reactive hepatitis	30	9	39

DISCUSSION

Presumably, there are several factors responsible for the pattern of tuberculosis as it is seen in elderly people. The changes coupled with the aging process undoubtedly influence the course of a tuberculous infection. Several writers have pointed out that the allergic manifestations of the disease are different at this time of life. Because of this alteration of the sensitivity to tuberculoprotein, the question naturally arises whether or not there is an accompanying decline in resistance or immunity.

It is quite significant that a high percentage of the kidneys and livers examined revealed changes of a significant degree. These changes consisted of various degrees of chronic inflammation in the kidney (figure 3*A*) which can be categorized under the general term of nephrosclerosis and chronic inflammatory reaction in the portal areas of the liver (figure 3*B*), which has been termed reactive hepatitis. Other organs, such as the thyroid and adrenals, also show various degrees of degenerative change in elderly people. The manner in which these disease entities would influence the host's ability to handle an infection such as tuberculosis is not known, but certainly they are of sufficient import to diminish function of the respective organs to some extent.

Heaf (8) suggested that the increased incidence of tuberculosis in elderly males might be due to changes in the endocrine system and, in particular, to the secretion of corticotropin. Certainly, some type of change in the endocrine system may be responsible for other disease processes in old people; for example, the marked increase in the incidence of cancer in the sixth, seventh, and eighth decades. Loeb (9) has

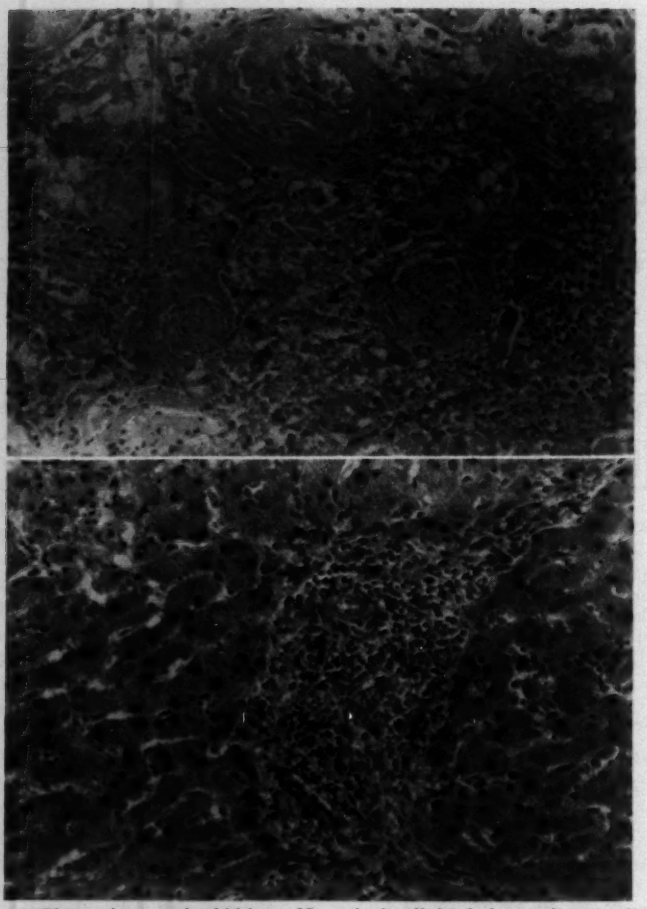

FIG. 3*A* (Upper). Photomicrograph of kidney. Note the hyalinized glomeruli and cellular infiltration. There is marked alteration of the vessel wall in the upper portion of the field.

FIG. 3*B* (Lower). Note the periportal infiltration of lymphocytes in this section of liver. There is some proliferation of fibrous tissue.

stated "that hormones are able to accelerate or intensify old age changes and to retard or even reverse certain others, and that the same hormone may induce both these effects under varying conditions."

Another factor affecting the course of pulmonary tuberculosis in elderly people is pulmonary fibrosis. There is not only alteration of the lung structure per se, but of the bronchial mucosa, blood vessels, and lymphatics as well. The degree of involvement varies from patchy areas of fibrosis (usually apical) to a diffuse bilateral process. In some instances, these changes could be attributed to antecedent respiratory disease, but in most cases they were considered idiopathic.

One of the striking observations in this study was the large number of patients in whom malignant tumors were discovered in addition to the tuberculous infection. The effects of a malignant lesion upon the course of an infection such as tuberculosis are undoubtedly many fold, but in the lung there is definite evidence that the cancer can actually invade walled-off or

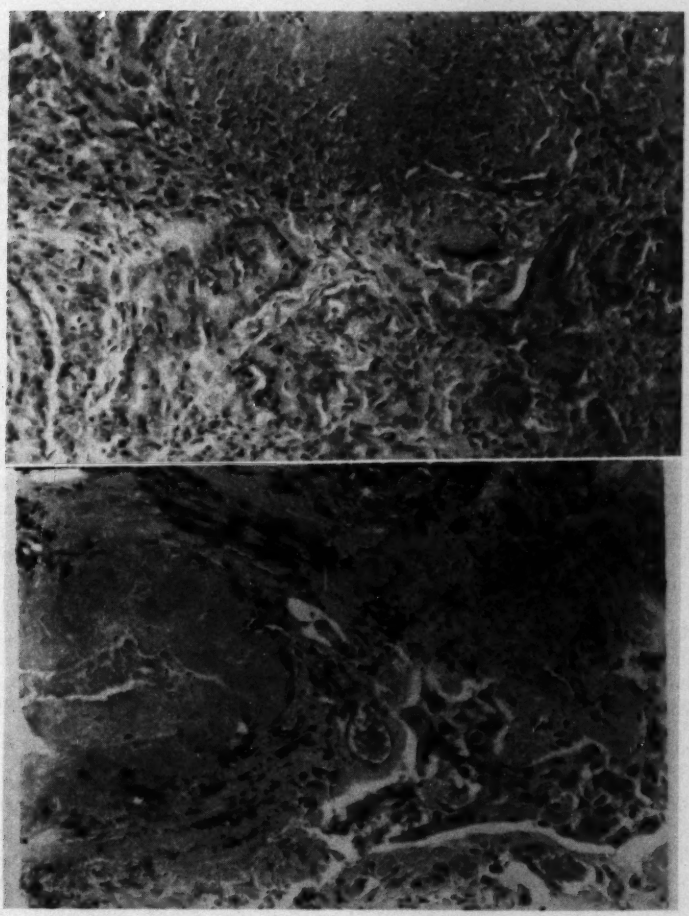

FIG. 3*C* (Upper). Photomicrograph of the lung. Most of the field is occupied by tumor, but in the upper central zone, there is a tuberculous focus with one Langhans' type of giant cell noted.

FIG. 3*D* (Lower). Photomicrograph of another lung showing pleomorphic tumor cells invading an area of dense fibrous tissue containing carbon pigment. A small area of necrosis is seen on the left.

quiescent tuberculous foci and reactivate them (figures *3C* and *3D*). Aside from the invasiveness of the cancer, there are secondary or indirect effects which alter the status of a tuberculous infection, i.e., nutritional problems, secondary anemia, invasion of other organs, et cetera. Of the 18 cases of extrapulmonary carcinoma, about one-half were primary in the gastrointestinal tract (table 2). Metastatic lesions in the lungs are prone to invade quiescent tuberculous foci in the same way as primary bronchogenic cancers.

In addition to the above features, uncontrolled diabetes mellitus, peptic ulcer, cirrhosis of the liver, chronic alcoholism, dietary or nutritional factors, housing, and occupational hazards should be mentioned when discussing the course of tuberculous infection in old people.

Most of the present cases of tuberculosis in elderly people were uncovered quite by accident. Usually there was some other ailment that prompted the patient to consult a physician and, in the course of a diagnostic study, the tuberculous lesion in the lung was discovered. Doubtless

TABLE 2

EIGHTEEN CASES OF EXTRAPULMONARY CARCINOMA COEXISTING WITH PULMONARY TUBERCULOSIS*

Primary Site	Number of Cases
Stomach	4
Pancreas	4
Kidney	3
Esophagus	2
Breast	2
Colon	1
Prostate	1
Tongue	1
Total	18

* This is a breakdown of the extrapulmonary cancers by systems. Note that the majority are in the gastrointestinal tract.

many cases have been overlooked in the past because the patient's complaints were minimized, and the signs and symptoms were attributed to some other clinical entity. That it is important to recognize active tuberculosis in the elderly goes without saying because of the necessity for treatment and also because of the fact that it may point out some underlying or smouldering condition which has reactivated a quiescent lesion.

SUMMARY

Eighty-nine patients more than seventy years of age showed evidence of pulmonary tuberculosis at autopsy. Tubercle bacilli were demonstrated in the majority of the cases. Associated with the pulmonary tuberculosis were other conditions, such as benign nephrosclerosis and hepatitis. Of greatest significance was the fact that some 33 patients also had cancer, 15 cases of which had arisen in the pulmonary structures.

SUMARIO

La Tuberculosis Pulmonar en los Ancianos

Ochenta y nueve sujetos de más de setenta años de edad revelaron en la autopsia signos de tuberculosis pulmonar. En la mayoría, se obtuvo una bacteriología positiva. Junto con esta tuberculosis pulmonar había otras dolencias, tales como nefrosclerosis benigna y hepatitis reactiva; pero de mayor importancia fué el hecho de que unos 33 enfermos tenían además cáncer: en 15 pulmonar y en 18 extrapulmonar.

RESUME

Tuberculose pulmonaire chez les gens agés

Quatre vingt neuf malades au-dessus de soixante dix ans montrèrent l'évidence de tuberculose pulmonaire à l'autopsie. On obtint une bactériologie positive dans la plupart des cas. Il y avait d'autres maladies assoçiées à cette tuberculose pulmonaire, telles qu'une néphrosclérose bénigne et une hépatite réactionnelle; mais, d'une plus grande signification, il y eut le fait que 33 malades avaient aussi un cancer: 15 cancers pulmonaires et 18 extrapulmonaires.

REFERENCES

(1) MEDLAR, E. M., SPAIN, D. M., AND HOLLIDAY, R. W.: Disregarded seedbed of the tubercle bacillus, Arch Int Med, 1948, *81*, 501.

(2) MYERS, J. A.: Tuberculosis lurks among the aged, Geriatrics, 1952, *7*, 324.

(3) BARBER, L. M.: Tuberculosis: A geriatric problem, Geriatrics, 1953, *8*, 306.

(4) WILKINS, E. G.: Incidence and onset of pulmonary tuberculosis in old men, Brit J Med, 1956, *1*, 883.

(5) AMAZON, P.: Tuberculin reaction in old age, Amer Rev Tuberc, 1943, *47*, 41.

(6) BERESFORD, O. D.: Tuberculin skin sensitivity in old age, Amer Rev Tuberc, 1958, *77*, 323.

(7) CHESROW, E. J., AND NOVAK, J. B.: Tuberculin testing of the aged, Dis Chest, 1957, *32*, 217.

(8) HEAF, F. R. C.: Tuberculosis in geriatrics, J Roy Inst Public Health, 1955, *18*, 325.

(9) LOEB, L.: Harvey Lectures, 1940, *36*, 228.

THE BINDING CAPACITY OF TUBERCULOUS AND NONTUBERCULOUS HUMAN SERUM FOR I^{131}-LABELED EXTRACTS FROM TUBERCLE BACILLI[1, 2]

RICHARD S. FARR AND HUBERT BLOCH

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INTRODUCTION

Patients and experimental animals infected with *M. tuberculosis* may have detectable circulating antibody to a number of mycobacterial antigens as well as delayed skin sensitivity to tuberculin (1). Tuberculin sensitivity can develop after minimal exposure to tubercle bacilli and persist for years in humans and animals. In contrast, circulating antibody responses to most antigens are characteristically more closely related to both the amount of antigen involved in the initial immunizing exposure and the length of time between the initial exposure and the time when the amount of antibody is measured.

The most frequently used technique for the detection of antibodies in tuberculous patients measures the agglutination of sensitized erythrocytes by serum antibodies (2). The average hemagglutination titer found in tuberculous patients is higher than the average titer found in nontuberculous healthy persons or in patients suffering from nontuberculous diseases. However, the data of these three groups overlap to such an extent that the titer that must be selected so as to exclude all false positives is so high that it also excludes 90 per cent of the known tuberculous cases (3).

The present preliminary study was undertaken in the belief that more sensitive methods for the direct measurement of antibodies might eventually lead to techniques permitting a better discrimination between the high contingent of false-positive reactions and more than 10 per cent of the patients suffering from tuberculosis.

The present study makes use of a relatively novel technique (4) for determining the binding capacity of serum for various antigens. Instead of a hemagglutination titer which indicates the minimal quantity of serum capable of agglutinating a certain suspension of sensitized erythrocytes, this technique determines the exact amount of antigen which is bound by a given volume of serum globulins. The antigens used were crude extracts of human tubercle bacilli. These preparations were labeled with I^{131} and incubated with the human test serum before precipitating the human globulin with rabbit anti-human globulin serum. When binding capacity was increased, the amounts of I^{131} precipitated were also increased as a result of specific bonds formed between the antigen and circulating antibody.

The present data indicate that the serum from approximately 40 per cent of patients with clinically significant tuberculosis had a higher binding capacity for I^{131}-labeled products of tubercle bacilli than the highest binding capacity found in serum from healthy persons or from patients with a variety of nontuberculous infections and other disease states. These results were encouraging because they seemed to indicate that the method might be a helpful tool in the study of the mechanisms underlying acquired resistance in tuberculosis. It may be well to emphasize, however, that at the present time this method is not suggested as another diagnostic test and no attempt was made, therefore, to compare the present results with those of recent clinical serologic studies on tuberculous patients (5, 6).

MATERIALS AND METHODS

Antigens: A variety of crude and purified antigens derived from tubercle bacilli were used. They were prepared as follows: Surface cultures of *M. tuberculosis*, strain H37Rv, were grown on Sauton medium and harvested after three to four weeks' growth. The cultures were washed with water on a Buchener funnel, ground in a mortar with approximately one volume of water and glass powder for about fifteen minutes, and sonicated in a sonic oscillator[3] for one hour. The sonicated material

[1] From the departments of Medicine and Microbiology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

[2] This study was supported by grants from The Health and Research Services Foundation (A-65), and the Institute of Allergy and Infectious Diseases (E-2104 and E-1513) of the National Institutes of Health, U. S. Public Health Service.

[3] Raytheon 10 kc. 200 watt output oscillator.

was then centrifuged at 4,000 r.p.m. for thirty minutes to sediment the glass powder and coarse bacterial debris. The supernatant was then centrifuged in a Servall centrifuge at top speed for one hour. The clear supernatant of this centrifugation was filtered through a Millipore filter and the filtrate lyophilized. The entire operation was carried out in the cold.

I^{131}-labeling of tuberculous antigen (I H37):* Ten-milligram samples of cell homogenates of the H37Rv strain of tubercle bacilli were labeled with I^{131} according to the method of Talmage and associates (7). The I^{131}-labeled cell homogenates were cleared of debris by centrifuging for thirty minutes at 50,000 × g in a Spinco preparative ultracentrifuge. The supernatants were analyzed for nitrogen and diluted so as to contain approximately 1.0 γ N per ml. of homogenate unless otherwise noted. The I* H37 antigen was diluted in 1:10 normal rabbit serum diluted in borate buffer containing 0.04 N unlabeled potassium iodide.

"Blocking antigens": Blocking antigens were used in order to test the specificity of the binding between serum and I* H37 antigens. The procedure consisted of adding excess of unlabeled H37 antigen to the serum prior to the addition of I* H37. Bondings blocked by this procedure were regarded as specific, in contrast to those which remained unblocked after this treatment. Twenty-five hundred micrograms of blocking antigen per 0.5 ml. borate buffer were used for all of the studies reported.

Preparation of rabbit anti-human globulin: New Zealand white rabbits were immunized with 10.0 mg. intravenous injections of normal human globulins three times a week for at least three weeks. Seven days after the last injection, the animals were bled and the sera pooled. The human globulin used to immunize the rabbits[4] contained alpha-, beta-, and gamma-globulins, and no chemical preservative was added.

Standardization of anti-human globulin sera: Since rabbit anti-human globulin contained antibodies against all of the human globulins and since it was not possible to determine the titer for each of the globulin components, the amount of rabbit anti-human globulin added was selected as one and one-half times the amount required to precipitate more than 90 per cent of the human gamma-globulin present in the human serum after two hours' incubation at 4°C. This was done by the method of Talmage and Maurer (8), using I^{131}-labeled human gamma-globulin (I* HGG) as antigen. One microgram of I* HGG N was added as a trace label to the dilution of human test serum to be precipitated by the rabbit anti-human globulin. The amount of anti-human globulin required was usually between 1.0 and 2.0 ml. Antiserum pools requiring more than 2.0 ml. were not used.

Human test serum: Serum was prepared from 10.0-ml. samples of clotted whole blood obtained from ward patients at Presbyterian Hospital or from Leech Farm Tuberculosis Sanitarium. Immediately after preparation, all serum specimens were stored at −20°C. until used. The diagnosis of active tuberculosis in most cases was made on the basis of a culture positive for tubercle bacilli from sputum, gastric washings, or biopsy material. In some instances, the diagnosis was made only on the basis of a smear positive for acid-fast bacilli obtained from sputum or body fluid, and the material was not cultured. Roentgenographic evidence was not used as the sole criterion for the presence of active tuberculosis. Tuberculin skin testing was performed on most tuberculous and nontuberculous patients. As will be noted below, the nontuberculous patient population contained only few supposedly healthy persons, because an effort was made to obtain serum from patients with a wide variety of acute and chronic clinical states which in any way could masquerade as tuberculosis.

Basic test procedure: Five-tenths-milliliter aliquots of a 1:40 dilution of the human serum to be tested were mixed with 0.5 ml. of either borate buffer or blocking antigen. Immediately after this addition, 0.5-ml. aliquots of I* H37 were added to both tubes and the tubes were incubated overnight at 4°C. On the following day, two 0.5-ml. aliquots were prepared from each of the two tubes and the globulins and globulin-I* H37 complexes were precipitated by the addition of appropriate amounts of rabbit anti-human globulin for two hours at 4°C. The precipitates formed were separated by centrifugation at 1,860 R.C.F. (relative centrifugal force) for forty-five minutes, and after one wash with 3.0 ml. cold borate buffer, the I^{131} activity present in the precipitate was determined in a gamma scintillation counter. The per cent of the original I^{131} activity precipitated was calculated by comparing the washed precipitate with an 0.5-ml. aliquot of a 1:3 dilution of the original antigen solution added. The per cent of I^{131} precipitated in the tubes containing borate buffer less the per cent I^{131} activity present in the tubes containing blocked antigen was taken as the per cent of I^{131} activity specifically bound by globulin that was presumably antibody.

Results

Experiments comparing the binding capacity of tuberculous and nontuberculous human serum for I H37:* The basic procedure was first applied to 27 specimens of serum from patients with active tuberculosis and 48 specimens from patients without detectable active tuberculosis, including 4 healthy persons. The I* H37 binding capacities of these serum specimens are presented in table 1. In order to provide full information regarding the test, this table lists the complete data obtained with and without the unlabeled blocking antigen added and the clinical diagnosis

[4] Kindly supplied by Lederle Laboratories.

TABLE 1

BINDING CAPACITY OF TUBERCULOUS AND NONTUBERCULOUS HUMAN SERUM FOR I*H37

Tuberculous Serum Number	Unblocked Per Cent Precipitated	Blocked Per Cent Precipitated	Unblocked minus Blocked	Smear for Acid-fast Bacilli	Culture for Acid-fast Bacilli	Guinea Pig Inoculum	First-Strength PPD	Second-Strength PPD	OT	Clinical Diagnoses
25*	17.25	3.23	14.02	+	+	ND	−	−	−1:10	Tuberculosis, pulmonary and miliary; diabetes mellitus; uremia
23*	17.41	3.45	13.96	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
19*	14.68	2.57	12.11	+	+	−	ND	ND	ND	Tuberculosis, pulmonary and costal cage, sinus tract
71*	15.25	3.53	11.72	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
66*	15.00	3.46	11.54	+	+	ND	ND	ND	ND	Tuberculosis; silicosis; allergic to penicillin
39*	13.88	2.62	11.21	+	+	+	−	+	ND	Tuberculosis, spondylitic, with retroperitoneal abscess
21*	12.16	2.37	9.79	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
22*	11.75	2.61	9.14	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
67*	12.20	3.14	9.06	+	+	ND	ND	ND	+	Tuberculosis, pulmonary; silicosis
4*	10.92	2.70	8.22	+	+	+	ND	ND	+1:10,000	Tuberculosis, pulmonary; multiple myeloma
68*	11.87	3.96	7.91	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; anemia, hypochromic, microcytic
70*	11.70	3.95	7.75	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; arteriosclerotic heart disease; hypertension
74	9.88	2.96	6.92	−	−	ND	−	+	ND	Arthritis, rheumatoid; anthracosilicosis
78	10.05	3.13	6.92	−	−	−	−	−	−1:10	Bronchopneumonia; chronic bronchitis
43	10.03	3.20	6.83	ND	ND	ND	ND	ND	ND	Cholecystitis; cholelithiasis; hepatic cirrhosis
1*	9.36	2.74	6.62	+	−	+	ND	ND	ND	Tuberculosis, miliary with secondary Addison's disease
65*	9.48	2.89	6.59	−	+	ND	ND	ND	+	Tuberculosis, pulmonary and laryngeal
16*	9.53	2.96	6.57	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; squamous cell carcinoma of nasal septum
18*	9.79	3.36	6.43	+	+	−	+	ND	ND	Tuberculosis, pulmonary
63	9.64	3.35	6.29	ND	ND	ND	ND	ND	ND	Syphilis, tabes dorsalis, Charcot's joint disease
51	8.68	2.53	6.15	ND	ND	ND	ND	ND	ND	Arthritis, rheumatoid
72*	9.29	3.16	6.13	−	−	ND	ND	ND	+	Tuberculosis, pulmonary; allergic to penicillin
107	9.37	3.26	6.11	ND	ND	ND	−	+	ND	Arteriosclerotic heart disease; adenocarcinoma of rectum
41*	8.70	3.06	5.64	+	+	+	−	−	ND	Tuberculosis, miliary
14*	8.35	2.91	5.44	+	+	ND	+	ND	ND	Tuberculosis, pulmonary
114*	8.76	3.60	5.16	+	+	+	−	+	ND	Tuberculosis, spondylitic
38*	8.08	2.96	5.12	+	−	ND	+	ND	ND	Tuberculous adenitis
29	7.74	2.69	5.05	ND	ND	ND	ND	ND	ND	Dermatomyositis; lupus erythematosus; disseminated hypergammaglobulinemia
20*	8.25	3.26	4.99	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; anemia
143	7.70	3.14	4.56	ND	ND	ND	ND	ND	+1:10,000	Duodenal ulcer; obstructive emphysema

TABLE 1—CONTINUED

Tuberculous Serum Number	Unblocked Per Cent Precipitated	Blocked Per Cent Precipitated	Unblocked minus Blocked	Smear for Acid-fast Bacilli	Culture for Acid-fast Bacilli	Guinea Pig Inoculum	First-Strength PPD	Second-Strength PPD	OT	Clinical Diagnosis
24*	6.83	2.44	4.39	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
11	6.86	2.63	4.23	ND	ND	ND	+	ND	ND	Normal male
69*	7.51	3.44	4.07	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; syphilis
10	6.98	3.15	3.83	–	–	ND	–	+	ND	Argentaffinoma broncho-pneumonia
57	6.38	2.55	3.83	–	–	–	–	+	ND	Lupus erythematosus, disseminated; miliary tuberculosis, suspected
50	6.36	2.58	3.78	–	–	ND	–	+	+1:10,000	Actinomycosis (+ culture) with pleural effusion
42	6.41	2.67	3.74	ND	ND	ND	ND	ND	ND	Amyotrophic lateral sclerosis
80	6.53	2.87	3.66	–	–	ND	–	+	ND	Renal disease (chronic glomerulonephritis suspected)
60	6.41	2.83	3.58	ND	ND	ND	ND	ND	ND	Lupus erythematosus, disseminated
58	6.83	3.26	3.57	–	ND	ND	ND	+	ND	Arthritis, gouty; syphilis
48	5.95	2.43	3.52	ND	ND	ND	ND	+	ND	Pyelonephritis, chronic (*E. coli*)
53	6.31	2.80	3.51	–	–	ND	–	–	ND	Lupus erythematosus, disseminated
106	7.10	3.60	3.50	ND	ND	ND	–	+	ND	Chronic interstitial pancreatitis with pancreatic insufficiency
27	5.58	2.47	3.11	ND	ND	ND	ND	ND	ND	Serum sickness (horse)
64	5.55	2.53	3.02	–	ND	ND	ND	ND	ND	Pneumonia, hepatitis, pancreatitis, renal tubular necrosis, all acute
31	6.13	3.13	3.00	–	–	ND	+	ND	ND	Lobar pneumonia, bacterial; bronchiectasis
55	5.72	2.74	2.98	ND	ND	ND	ND	ND	ND	Arthritis, gouty; peptic ulcer
76*	6.07	3.30	2.77	–	–	ND	–	+	ND	Tuberculous spondylitis; paroxysmal atrial fibrillation
34	5.25	2.49	2.76	ND	ND	ND	ND	ND	ND	Syphilis, tertiary (central nervous system)
56	5.08	2.37	2.71	–	–	ND	ND	ND	ND	Arthritis, rheumatoid
5	5.77	3.08	2.69	–	–	ND	+	ND	ND	Asthmatic bronchitis; pneumoconiosis
104	6.01	3.37	2.64	ND	ND	ND	+	+	ND	Thyroiditis, chronic; hypothyroidism; hypergammaglobulinemia (Sjogren's)
12	5.27	2.63	2.64	ND	ND	ND	–	–	– Patch	Normal child
59	5.45	2.83	2.62	ND	ND	ND	ND	ND	ND	Arthritis, rheumatoid
77*	5.25	2.72	2.53	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary; squamous cell carcinoma, mouth
62	5.68	3.16	2.52	ND	ND	ND	ND	ND	ND	Lupus erythematosus, disseminated
116	6.43	3.96	2.47	–	–	–	–	ND	ND	Echinococcal cyst, pulmonary
33*	5.61	3.26	2.35	–	–	+	ND	ND	+1:1,000	Tuberculosis, pulmonary
54	5.26	3.00	2.26	ND	ND	ND	ND	ND	ND	Arthritis, rheumatoid
30	6.34	4.19	2.15	ND	ND	ND	+	ND	ND	Tonsillitis, pharyngitis, anemia
3	4.66	2.55	2.11	ND	ND	ND	–	+	ND	Normal female
79	5.52	3.43	2.09	–	–	ND	–	ND	ND	Hypertensive cardiovascular disease

TABLE 1—CONTINUED

Tuberculous Serum Number	Unblocked Per Cent Precipitated	Blocked Per Cent Precipitated	Unblocked minus Blocked	Smear for Acid-fast Bacilli	Culture for Acid-fast Bacilli	Guinea Pig Inoculum	First-Strength PPD	Second-Strength PPD	OT	Clinical Diagnosis
52	4.69	2.67	2.02	ND	ND	ND	ND	ND	ND	Lupus erythematosus, disseminated
61	4.16	2.17	1.99	ND	ND	ND	ND	ND	ND	Arthritis, rheumatoid
8	4.23	2.25	1.98	ND	ND	ND	ND	ND	−1:1,000	Pharyngitis, pneumococcal; gastroenteritis
117	5.07	3.16	1.91	ND	ND	ND	−	+	ND	Diabetes mellitus
105	4.72	2.83	1.89	−	ND	ND	−	+	ND	Arteriosclerosis generalized; syphilis
36	4.54	2.65	1.89	ND	ND	ND	ND	ND	ND	Glomerulonephritis, acute; rheumatic fever, acute
37	4.73	3.02	1.71	ND	ND	ND	ND	ND	ND	Diabetes mellitus; diverticulosis
40	4.32	2.67	1.65	−	−	ND	−	−	ND	Erythema multiforme exudativum; Stevens-Johnson syndrome
7	4.47	2.85	1.62	−	−	ND	ND	ND	ND	Anemia, normocytic, ? etiology
49	4.12	2.54	1.58	ND	ND	ND	−	+	ND	Nephrotic syndrome (chronic glomerulonephritis suspected)
26*	4.55	3.04	1.51	+	+	ND	ND	ND	ND	Tuberculosis, pulmonary
6	4.20	2.95	1.25	ND	ND	ND	ND	ND	ND	Anemia, hemolytic; leukemia suspected
9	3.79	2.68	1.11	ND	ND	ND	ND	ND	− Patch	Tonsillar hypertrophy

* Indicates confirmed clinical diagnosis of tuberculosis
\+ Indicates positive reaction or finding
− Indicates negative reaction or finding
ND Indicates not done
For other explanations—*see* text

of each case. In subsequent tables, only the calculated specific binding capacity for the sera in question will be given. The data are arranged sequentially from the highest to the lowest observed per cent I* H37 specifically bound. Ideally, the 27 serum specimens with the highest I* H37 binding capacity should have been from the patients with active tuberculosis, but it may be seen that only 21 of the first 27 serum specimens were from patients with detectable tuberculosis. The 6 nontuberculous patients with relatively high I* H37 binding capacity represented one case of late syphilis complicated by Charcot joint disease, 2 cases of rheumatoid arthritis, one case of bronchopneumonia, one case of adenocarcinoma of the rectum, and one case of portal cirrhosis. Rheumatoid arthritis and/or systemic lupus erythematosus do not routinely give high I* H37 binding capacity, as may be seen from other similar cases in the control series which did not have particularly high values. Likewise, 4 other cases of syphilis which have been studied did not give particularly high binding values.

It may also be seen in table 1 that the high binding capacity for I* H37 was not dependent upon tuberculin reactivity. Many of the tuberculous and nontuberculous patients with strongly positive tuberculin skin tests had relatively low I* H37 binding capacity. The converse was also true in that serum No. 25, from a patient with miliary tuberculosis associated with diabetes, had the highest binding capacity for I* H37 associated with a negative skin test with first-strength PPD, second-strength PPD, and OT, 1:10.

The effect of various I H37 antigen preparations on the observed binding capacity with serum from tuberculous and nontuberculous patients:* It became apparent during the early phases of this study that different lots of I* H37 had different binding characteristics for particular tuberculous or nontuberculous serum. However, the relative difference between the binding capacity of an antigen for tuberculous and nontuberculous

serum remained relatively constant. Therefore, it was decided to use two of the nontuberculous serum specimens with high binding capacities as negative controls and two of the tuberculous specimens with definitely increased I* H37 binding capacity as positive controls for each test performed with various lots of I* H37. For this purpose, sera No. 51 and No. 63 were selected as negative controls and serum No. 25 as the positive control (*see* table 1).

The results obtained with these three serum specimens with six different lots of I* H37 are presented in table 2. The right-hand column in this table demonstrates that, when an average of the two nontuberculous serum controls were taken as unity, serum No. 25 had between 1.9 and 2.8 times more binding capacity than did the negative controls. This degree of correlation was in spite of the fact that the average binding by the high nontuberculous controls ranged from 3.5 to 10.4 per cent. The need to relate the binding capacity of an unknown serum to the binding capacity observed with the high negative controls is clearly indicated in table 2. To facilitate discussion in subsequent sections of this report, the ratio between the test serum and the negative controls has been designated as the binding ratio.

The binding ratios of the serum from 88 tuberculous and 63 nontuberculous patients: The binding ratios obtained on 88 tuberculous and 63 nontuberculous serum specimens (of which 27 and 48, respectively, appeared also in table 1) are presented in table 3. Six different preparations of I* H37 antigen were used during the collection of these data. The nontuberculous control group contained a broad spectrum of clinical states, including acute and chronic bacterial pulmonary infections, actinomycosis, Löffler's syndrome, echinococcal cyst of the lung, acute appendicitis, acute and chronic renal infections, syphilis, myocardial infarction, diabetes, multiple myeloma, systemic lupus erythematosus, rheumatoid arthritis, and gout. Most of the tuberculous group consisted of patients with proved clinically active pulmonary tuberculosis, but a few of the tuberculous cases represented such entities as tuberculous psoas abscess, tuberculous lymphadenitis, and tuberculous spondylitis.

It may be seen in table 3 that all of the nontuberculous serum specimens have a binding ratio of less than 1.20, the highest actually being the 1.11 observed with the serum of a case of rheumatoid arthritis (No. 74, table 1). Conversely, 100 per cent of the serum with ratios above 1.20 was from patients who had clinically significant tuberculosis, and this group constituted approximately 40 per cent of the patients

TABLE 2

BINDING CAPACITY OF NEGATIVE AND POSITIVE CONTROL SERUM FOR VARIOUS I*H37 ANTIGEN PREPARATIONS

Antigen Preparation	High Negative Controls		Average of High Negative Controls	Positive Control Serum 25	Ratio of Positive Control to Negative Controls
	Serum 51	Serum 63			
A	12.2	8.6	10.4	19.7	1.9
240	8.6	7.9	8.2	17.6	2.1
LF-R	7.2	6.9	7.1	16.5	2.3
256	6.7	6.3	6.5	15.8	2.4
B	6.2	6.3	6.2	14.0	2.2
194	4.7	5.4	5.0	12.6	2.5
200	3.0	4.1	3.5	9.8	2.8

TABLE 3

DISTRIBUTION OF BINDING RATIOS OF SERUM FROM TUBERCULOUS AND NONTUBERCULOUS PATIENTS

Specific Binding Index	Without Active Tuberculosis			With Active Tuberculosis		
	Number of Cases	Per Cent of Total	Cumulative Per Cent of Total	Number of Cases	Per Cent of Total	Cumulative Per Cent of Total
0.00–0.15	1	1.6	1.6	3	3.4	3.4
0.16–0.30	11	17.5	19.1	3	3.4	6.8
0.31–0.45	17	27.0	46.0	6	6.8	13.6
0.46–0.60	16	25.4	71.4	6	6.8	20.4
0.61–0.75	9	14.3	85.7	4	4.5	25.0
0.76–0.90	2	3.2	89.0	14	15.9	40.9
0.91–1.05	4	6.3	95.2	10	11.4	52.3
1.06–1.20	3	4.8	100.0	5	5.7	57.9
1.21–1.35	0	—	100.0	9	10.2	68.2
1.36–1.50	0	—	100.0	3	3.4	71.6
1.51–1.65	0	—	100.0	5	5.7	77.3
1.66–1.80	0	—	100.0	4	4.5	81.8
1.81–1.95	0	—	100.0	4	4.5	86.4
1.96–2.10	0	—	100.0	1	1.1	87.5
2.11–2.25	0	—	100.0	3	3.4	90.9
2.26–2.40	0	—	100.0	1	1.1	92.0
2.41–2.55	0	—	100.0	4	4.5	96.6
2.56–2.70	0	—	100.0	1	1.1	97.7
2.71–2.85	0	—	100.0	0	—	97.7
2.86–3.00	0	—	100.0	1	1.1	98.9
3.01–3.15	0	—	100.0	1	1.1	100.0
Total...	63	100.1		88	99.6	

with active tuberculosis. The patients with ratios between 1.20 and 0.90 (17 per cent of the serum from tuberculous patients and 11 per cent from the nontuberculous patients) were also of particular interest in view of the fact that more tuberculous patients than nontuberculous patients fell within this range. The seven nontuberculous serum specimens with ratios between 0.90 and 1.11 represented serum from the two high negative controls used to establish the ratio: No. 74, mentioned above; No. 78, a case of Staphylococcus and Hemophilus pneumonia; No. 43, a case of portal cirrhosis; No. 107, a case of adenocarcinoma of the rectum; and No. 113, a diabetic with gangrene of the foot. All but the last mentioned are included in table 1.

Discussion

Mycobacterium tuberculosis possesses a large number of cellular constituents which are known to be antigenic and cause the formation of circulating antibodies (1). Most of these antibodies make their appearance in the course of a tuberculous infection and can be detected by a variety of immunologic techniques. Some are specific, i.e., the antigens reacting with these antibodies occur only in *M. tuberculosis*. Others react with antigens which appear to be shared by a variety of mycobacteria.

Although protection against tuberculosis has yet to be connected with circulating antibody, it would not seem unreasonable to assume that the quantity and avidity of antibody may play a part in protection. Also, the amount of antibody present in a patient might be directly related to the amount of antigenic material to which the patient was exposed. In other words, the amount of antibody might reflect the degree of tuberculous infection.

Most serologic techniques which have been used in the determination of antibodies against antigens from tubercle bacilli suffer from a common defect: they are not strictly quantitative methods, giving only approximate indications of the actual concentration of antibodies in a test serum.

The method which was used in the present study measures directly the binding capacity of serum antibodies for bacterial antigens. The specific binding capacity can be expressed in accurate numbers which makes this method different from all previous ones. In an attempt to comprise the broadest possible spectrum of antibodies against constituents of tubercle bacilli, crude bacterial extracts were used. These extracts were labeled with I^{131}. It was impossible to tell whether some antigenic components were labeled preferentially or whether all of the label was actually fixed to antigenic components. It is clearly necessary to purify the antigens further and to label the various purified fractions for parallel testing with the same test serum. Supposedly, such a procedure will eliminate some components as nonantigenic while others might turn out to have higher—and perhaps more specific—binding capacities. It is likely that the quantitative aspects of the method will prove particularly useful in the course of such purification.

Despite many efforts by numerous investigators, no single antibody has yet been found in tuberculous patients which does not occur also in some healthy persons or in patients suffering from nontuberculous disease. The results of the present study are no exception. However, the quantitative aspects of the method permit the complete elimination of false positive reactors by establishing empirically the maximal binding capacity occurring in serum from nontuberculous patients. The data so far obtained by the use of the binding ratio described in this report can be summarized as follows: (*1*) a ratio above 1.20 was always indicative of active tuberculosis and was observed in approximately 40 per cent of the serum from cases of active tuberculosis; (*2*) a ratio between 0.90 and 1.20 was indicative of at least a 50 per cent chance that the serum came

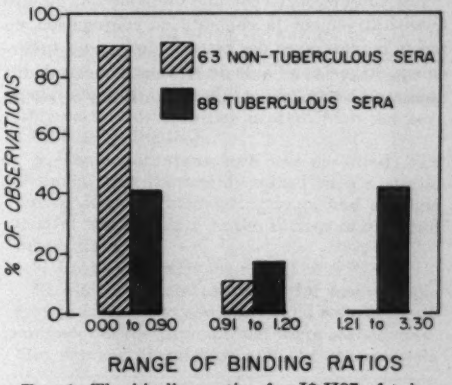

Fig. 1. The binding ratios for I* H37 of tuberculous and nontuberculous serum specimens.

from a case of active tuberculosis; (*3*) a ratio of less than 0.90 was essentially noninformative with respect to the presence or absence of active tuberculosis; it was observed in approximately 40 per cent of the cases of known active tuberculosis and in 90 per cent of the serum from nontuberculous patients. These relationships are shown graphically in figure 1.

Summary

A method is described which measures quantitatively the binding capacity of human serum for I^{131}-labeled extracts from tubercle bacilli. The method was applied to an analysis of 151 specimens of serum from known tuberculous and nontuberculous patients and from healthy subjects.

Sumario

La Capacidad Fijadora del Suero Tuberculoso y No Tuberculoso para los Extractos I^{131}-Rotulados de Bacilos Tuberculosos

Se describe un método que mide cunatitativamente la capacidad fijadora del suero humano para los extractos I^{131}-rotulados de bacilos tuberculosos. El método fué aplicado al análisis de 151 ejemplares de suero procedente de enfermos reconocidamente tuberculosos y no tuberculosos y de sujetos sanos.

Resume

La capacité de conjugaison de sérum humain tuberculeux et non tuberculeux avec des extraits de bacilles tuberculeux étiquetés à l'aide de I^{131}

Les auteurs décrivent une méthode qui mesure quantitativement la capacité de conjugaison du sérum humain avec des extraits de bacilles tuberculeux étiquetés à l'aide de I^{131}. Cette méthode fut appliquée à l'analyse de 151 échantillons de sérum issu de tuberculeux avérés et de sujets en bonne santé.

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REFERENCES

(1) Boyden, S. V.: The immunological response to antigens of the tubercle bacillus: Some experimental aspects, Progr Allergy, 1958, *5*, 149.

(2) Middlebrook, G., and Dubos, R.: Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli, J Exp Med, 1948, *88*, 521.

(3) Gernez-Rieux, Ch., and Tacquet, A.: Les réactions d'hémagglutination et d'hémolyse conditionnée dans la tuberculose, Advance Tuberc Res, 1952, *5*, 66.

(4) Feinberg, R.: Studies on nonprecipitating antibody coexisting with precipitating antibody: I. Production of a "blocking type" antibody in rabbits, J Immunol, 1958, *81*, 14.

(5) Parlett, R. C., and Youmans, G. P.: An evaluation of the specificity and sensitivity of a gel double-diffusion test for tuberculosis, Amer Rev Resp Dis, 1959, *80*, 153.

(6) Thurston, J. R., and Steenken, W., Jr.: Comparison of gel precipitin and sensitized erythrocyte techniques for the detection of antibody in the serum of tuberculous and nontuberculous patients, Amer Rev Resp Dis, 1960, *81*, 695.

(7) Talmage, D. W., Dixon, F. J., Bukantz, S. C., and Dammin, G. J.: Antigen elimination from the blood as an early manifestation of the immune response, J Immunol, 1951, *67*, 243.

(8) Talmage, D. W., and Maurer, P. H.: I^{131}-labelled antigen precipitation as a measure of quantity and quality of antibody, J. Infect Dis, 1953, *92*, 288.

A CULTURAL STUDY OF ACID-FAST MICROORGANISMS CONCENTRATED BY HYDROCARBON-ADSORPTION AND SEDIMENTATION METHODS[1]

SANFORD CHODOSH[2] AND JAMES B. GRAY

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Introduction

The evaluation of a new micro-culture method for the isolation and identification of acid-fast microorganisms from sputum has recently been reported from this laboratory (1). The well-known hydrophobic and lipophilic nature of acid-fast organisms was utilized for the concentration from the sputum of these organisms on a cover-slip prepared with a siliconized layer. The prepared cover-slips were sufficiently long so that acid-fast organisms could be harvested from all depths of the digested and homogenized specimen. Many controls were used for comparison with this cover-slip culture method. In this particular experiment, a comparison was made between the growth obtained from the centrifuged sediment of the sputum specimen digested and homogenized with trisodium phosphate with the growth obtained from the surface of the supernatant portion of the same specimen. The results obtained from this set of controls seemed to be of sufficient interest to warrant this separate report.

Materials and Methods

Sputum specimens were collected consecutively from patients with chronic and acute pulmonary disease admitted to the South Department of the Boston City Hospital. The specimens were collected in new clean glass bottles with new cork stoppers. Approximately 30 ml., or, if less, the total twenty-four-hour sample was usually obtained. These daily specimens were given code numbers and were immediately frozen and maintained at −4°C. Specimens were collected over a period of several months in this manner. The samples examined on any particular experiment day were thawed and handled immediately.

Two hundred and forty sputum specimens were selected at random. The volumes varied from 0.5 to 12 ml., but most of the specimens were from 6 to 10 ml. They were processed as described below:

1. The specimen was placed into sterile, 30-ml. screw-capped glass bottles.
2. An equal volume of a 10 per cent aqueous solution of trisodium phosphate was added.
3. The mixture was digested and homogenized in an automatic shaker apparatus for fifteen to forty-five minutes at room temperature.
4. This homogenate was then poured into sterile conical 15-ml. centrifuge tubes.
5. A solid paraffin ball, 2 mm. in diameter, was added to each centrifuge tube. This remained floating at all times. These paraffin balls were prepared in the following manner: household sealing paraffin[3] was purified by melting the solid paraffin, mixing in Norite A in excess, and stirring for two to three minutes. Ninety-five per cent ethanol was slowly added. The carbon settled out in the ethanol layer and, after solidification, the paraffin was removed. The paraffin was then remelted. Using a dropper, the liquid paraffin was added dropwise to cool 95 per cent ethanol. With practice, uniform paraffin spheres could be obtained. These were used directly from the 95 per cent ethanol, in which they had been stored.
6. The homogenized sputum, with the floating paraffin ball, was then centrifuged for ten minutes at 5 g. This effected a good separation of the visible solid materials from the clear supernatant fluid.
7. The paraffin ball was gently fished from the surface of the supernatant fluid with a sterile loop and streaked along the surface of a single Peizer slant in a screw-capped tube. The paraffin ball was left on the surface of the medium. A small amount of the surface fluid was unavoidably carried over to the medium with the paraffin ball by the loop.
8. The supernatant fluid was decanted. The sediment was thoroughly mixed with a sterile 2-mm. 24-gauge inoculating loop, and a single loopful was streaked on the surface of a second Peizer slant.
9. Both tubes were incubated at 37°C.
10. Cultures were examined for macroscopic growth after twenty-one days and were then examined weekly through the forty-second day. The number of colonies and the macroscopic

[1] From the Department of Medicine, Tufts University School of Medicine, and Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts; and the Institute of Laboratories of the Massachusetts Department of Public Health, Jamaica Plain, Massachusetts.

[2] Resident Fellow in Medicine, Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts; and Resident Fellow, National Tuberculosis Association.

[3] Esso brand.

colonial characteristics of discrete colonies were recorded at forty-two days.

11. Microscopic examinations of the peripheral growth were made in most instances. These were made with a wet staining method. A small portion of the growth was placed in a drop of 1:4000 crystal-violet solution prepared in a M/15 Sørensen's buffer at pH 7.2. This preparation was gently warmed and a cover-slip applied. Orientation and staining of the bacilli were recorded from these observations. The peripheral colonial architecture was nicely maintained by this technique.

Results

Sensitivity of Method

Two hundred and forty specimens of sputum were cultured, making a total of 480 culture slants. One hundred of the 240 specimens were positive for the growth of acid-fast microorganisms by one or both methods used. Ninety-five of these were positive for the growth of mycobacteria and 5 were positive for Nocardia or Nocardia-like organisms.

An analysis of the 95 specimens positive for growth of mycobacteria and the degree of recovery is presented in table 1. Seventy (73.7 per cent) of these specimens had growth of mycobacteria by both methods. Eighty-eight (92.6 per cent) were positive on the sediment-streak (S) slants and seventy-seven (81.0 per cent) were positive on the paraffin-ball (PB) slants.

TABLE 1

Comparative Degrees of Recovery of Mycobacteria by Culture from 95 Sputum Specimens by the Two Concentration Methods

Sediment versus Paraffin-Ball

Degree Positive*	Paraffin-Ball Culture (PB)				
	3+	2+	1+	0	Total
Sediment-streaked culture (S)					
3+	9	7	11	4	31
2+	1	8	14	2	25
1+	1	1	18	12	32
0	1	1	5	145	152
Total	12	17	48	163	240

* Degree positive:
3+ = innumerable colonies
2+ = 11 to 100 colonies
1+ = 1 to 10 colonies
0 = no growth or contamination

It is clear from table 1 that the sediment-streak-concentrated cultures provided a greater recovery of organisms than did the paraffin-ball cultures. Whereas 56 of 88 (64 per cent) of the positive sediment-streak-cultures had eleven or more colonies per slant, only 29 of 77 (38 per cent) of the paraffin-ball cultures had comparable numbers of colonies. However, if only the specimens that were strongly positive (3+) on sediment-streak-culture are considered, there is a greater number of strongly and moderately positive cultures by paraffin-ball culture than would be expected from the general distribution of positive cultures. There were nine specimens observed to be positive in the S-slant 3+ and PB slant 3+ category. If there were a random distribution of organisms in the specimen, the expected number of positives in this block should be 12 of 240 × 31 = 1.55 or approximately 2. In fact, under random conditions, the findings in the PB slants in the group of cultures strongly positive (3+) by S-slant should read PB 3+ = 2; 2+ = 2; 1+ = 6; 0 = 21 with a total = 31. This would imply that there was a much greater recovery by the PB concentration method from the strongly positive specimens than one would expect if the chance of recovering organisms by this method was determined by random distribution of acid-fast bacilli in the specimen.

There were 5 Nocardia or Nocardia-like organisms isolated. Two of these were recovered by both concentration methods. Four of the 5 were positive in the sediment-streaked slant and 3 were positive on the paraffin-ball slant. This is obviously too small a sample for analysis.

Only 7.4 per cent (7 of 95) S-slants were negative when the matching PB-slants were positive (table 2). The S-slants were contaminated in 5 of these 7 instances. The other 2 S-slants missed were positive on PB slants with ten or less colonies. However, there was no contamination of any of the 18 of 95 slants that were negative by PB-method but positive by S-method. Twelve of the 18 PB-slants missed were positive on S-slants with ten or less colonies.

Influence of Contamination

A comparison of the contamination rates provides interesting and significant data (table 2 and figure 1). Rather strict criteria are employed for determining contamination. Contamination is defined as the presence on a slant of any

TABLE 2

COMPARISON OF CONTAMINATED SLANTS BY THE TWO CONCENTRATION METHODS
Sediment versus Paraffin-Ball

	Paraffin-Ball Slant (PB)			
	Positive Culture for Mycobacteria	Positive for Contamination	Negative for Mycobacteria and Contamination	Totals
Sediment-streaked Slant (S)				
Positive culture for mycobacteria	70	0	18	88
Positive for contamination	5	3	18	26
Negative for mycobacteria and contamination	2	0	124	126
Totals	77	3	160	240

demonstrable growth other than that of acid-fast bacilli. Twenty-nine of the 480 slants inoculated by both methods were found to be contaminated. However, there was a disparity between the frequencies of contamination observed by the two methods. Whereas 26 of the 240 (10.8 per cent) S-slants were contaminated, only 3 of the 240 (1.25 per cent) PB-slants were contaminated. The corresponding S-slants of the 3 contaminated PB-slants were also contaminated (table 3). If this high contamination rate of the S-slants is taken into consideration in calculating the number of specimens expected to be positive if contamination were not present, it will be found that the percentage of specimens that should have been positive is 41.1 per cent. This means that, instead of the 88 of 240 specimens positive by the S-method, 99 of 240 should have been positive. Therefore, an estimated 11 of 99 (11 per cent) positive cultures were missed because of contamination. There is no significant difference between the estimated (on the basis of contamination rate) and observed positive PB-cultures.

Influence on Morphology

Upon evaluation of approximately 50 to 60 per cent of the positive culture slants, it was realized that a great variation existed between the morphology of the colonies found on the sediment-streak-slant as opposed to the corresponding paraffin-ball-slant. From this point on, the gross morphologic descriptions of the colonies and the results of the microscopic examinations were recorded in greater detail. Sufficient descriptive data were obtained from 26 of the 70 specimens that were positive by both concentration methods to permit comparison. It is quite evident from these data that the paraffin-ball method tended to harvest acid-fast microorganisms that, on primary isolation, had more virulent characteristics than the organisms harvested from the sediment. The inability to judge the degree of virulence of the colonies examined on the basis of their gross morphology was impressive. Although the finding of a pale buff or ground-glass color usually correlated with a high degree of cording, it was also noted in some colonies that had random growth or a low degree of cording. However, some were noted to have a very high degree of cording and perfectly

	Type of Concentration			
	Sediment	Per Cent	Paraffin-Ball	Per Cent
Positive cultures observed	$\left(\frac{88}{240} \times 100\%\right)$	= 38.7	$\left(\frac{77}{240} \times 100\%\right)$	= 32.1
Positive cultures expected	$\left(\frac{88}{240 - 26} \times 100\%\right)$	= 41.1	$\left(\frac{77}{240 - 7} \times 100\%\right)$	= 32.5
Expected loss of positives due to contamination		4.4		0.4
Contamination rate	$\left(\frac{26}{240} \times 100\%\right)$	= 10.8	$\left(\frac{3}{240} \times 100\%\right)$	= 1.25

FIG. 1. Cultures positive for mycobacteria adjusted for contamination rates.

TABLE 3

COMPARISON OF THE DEGREE OF MICROSCOPIC CORDING FROM THE PRIMARY ISOLATION OF PAIRED MYCOBACTERIA CULTURES OBTAINED FROM BOTH CONCENTRATION METHODS

Degree of Cording	Paraffin-Ball Cultures					Totals
	4+	3+	2+	1+	0	
Sediment-streaked Cultures						
4+	2			1		3
3+	4					4
2+	2	1	1			4
1+	4	2	1			7
0	3		1	1	3*	8
Totals	15	3	3	2	3	26

Degree of cording:
0 = random growth
4+ = tight cords
1–3+ = intermediate amounts of cording
* 2 of the 3 were Nocardia species.

typical individual cells of *Mycobacterium tuberculosis* var. *hominis*. Rough and smooth colonies again correlated erratically with microscopic cording. It has been well established that relative virulence of mycobacteria can best be judged morphologically by the degree of microscopic cording noted in the colony (2–16). Therefore, the degree of cording was used as the criterion for comparison. The degree of cording seen on microscopic examination of each pair of cultures from a single specimen is compared in table 3.

The degree of cording was equal in only 6 of the 26 paired cultures positive by both concentration methods. Two of these 6 were Nocardia-like organisms that displayed noncorded growth with primary and secondary branching and with rather typical individual bacilli. In only one instance was there greater cording in the colonies from the S-slant as opposed to that in the PB-slant. However, in 19 of the 26 paired cultures, a greater degree of cording was noted in the colonies harvested by the PB concentration method than by the centrifuged sediment method. In 12 of these 19, the difference in the degree of cording was of a magnitude of 2+ or more. Five of the cultures that displayed cording on the PB-slant showed only random growth on the S-slant.

The correlation between paraffin-ball surface concentration and cording, as opposed to the centrifuged sediment concentration and decreased or absent cording, was striking. This was further substantiated in the results obtained with the cover-slip microcolonial culture technique (1). This technique has previously been described. However, a summary of this cover-slip method follows:

The sputum specimen was digested by a mucolytic and proteolytic enzyme, and the digested material was kept in a homogenous state by rotating at 4 r.p.m. in a roller-drum at a 15° angle. Into this tube a long cover-slip was placed with a siliconized strip on one surface. The acid-fast microorganisms are attracted to this surface and adhere to it. The cover-slip is long enough so that all of the specimen comes into contact with some part of the siliconized surface. It is possible, therefore, to harvest organisms from all depths of the specimen and to determine microscopically the depth at which each organism was suspended.

After five days of incubation of this cover-slip in a modified Dubos serum medium containing very little Tween® 80, the preparation was stained and examined for microcolonies. Almost uniformly, the tightly corded colonies, typical of *Mycobacterium tuberculosis*, were noted at the top of the cover-slip, the part which had been bathed by the surface portion of the specimen. Conversely the colonies at the bottom end of the cover-slip were usually less corded and often demonstrated a random growth pattern.

DISCUSSION

The differences in the results obtained by the two concentration methods require explanation. The rate of recovery of mycobacteria from the surface, concentrated by means of paraffin, as opposed to the concentrated sediment, corroborates the results of Klein and associates (17). The sedimentation method is superior to surface harvesting when the number of specimens positive for mycobacteria and the number of colonies per slant are compared. The results of others (18–21) indicate the important role in concentrating methods of the relationship of the specific gravity of the tubercle bacilli in the specimen to that of the material in which they are suspended. Flotation methods (22, 23) utilize this differential in specific gravity to effect the concentration of tubercle bacilli.

The results of Ellerman and Erlandsen (18), when working with aqueous suspensions of this organism, indicate that factors other than specific gravity and viscosity are perhaps of greater

significance in the concentration of sputum specimens. The possibility that the presence of fine particulate matter in digested and/or homogenized sputum specimens may play an important role in carrying the bacilli downward into the sediment is supported by the improved concentration noted when a fine flocculant is introduced into the specimen prior to sedimentation (24). This possibility is also supported by the fact that sedimentation methods alone work very poorly in clinical specimens free of particulate matter, e.g., urine or cerebrospinal fluid, unless such particles can be introduced. Another possible factor is the action of the digestants, e.g., sodium hydroxide et cetera, on the capsule of the organism. This action may be one of changing the polarity of the normally nonpolar surface of the organisms or it may be one of removal of the capsule, in part or in total.

The discrepancy noted in the number of specimens positive on the paraffin-ball concentrated cultures in the group of specimens which had the greatest degree of recovery by the sedimentation-concentrated cultures is also worthy of comment. There are many more positives in the PB-slants in this group than would be expected from the general distribution of positives in the whole series. A ready explanation for this finding might be that in such strongly positive specimens there is a greater chance of some organisms being at the surface of the supernatant fluid. However, this would necessarily assume that the distribution of organisms in the homogenized specimen is not uniform. It is interesting that the specimens, almost uniformly, come from patients with very active disease.

Another explanation for this skewed distribution is worthy of consideration in relation to the other findings in this study. Since these specimens come from very active cases, it may be assumed that a greater proportion of the tubercle bacilli would be of a more virulent type than those coming from treated cases. The work of others (25, 26) indicates that such virulent organisms display a greater degree of hydrophobia and lipophilia. It would be expected, therefore, that such organisms would be found in the environment that is the least aqueous, namely, the surface of the specimen. Once the microbes were there, they would have a greater attraction for any hydrocarbon on the surface.

The fact that the characteristic of hydrocarbon affinity displayed by acid-fast microorganisms can be exploited for the concentration of such organisms is supported by numerous investigators utilizing both liquid (25–40) and solid (41–47) hydrocarbons. It has also been demonstrated that silicones attract these hydrophobic organisms (1, 48).

The disproportionate distribution noted in table 1 would seem to be related to the results outlined in table 3. These data indicate that, in many of the sputum specimens examined, there is a mixture of acid-fast bacilli which varies in the degree of cording displayed on primary isolation. The use of a hydrocarbon concentration method, in conjunction with a sedimentation method on the same digested and homogenized sample, in some manner divides this population of variants. Results of this nature have been reported in cultures of patients who have been on long-term therapy with antituberculous drugs. The differences in such instances have usually been explained on the basis of varying drug susceptibilities of the organisms. Unfortunately, drug-susceptibility tests have not been evaluated in the present series of isolated organisms. However, the vast majority of the patients whose specimens displayed this phenomenon were either not on therapy or had been on therapy only a few days. The possibility that these patients had acquired a "mixed" infection cannot at this time be excluded.

The possibility must also be considered that this difference is due to an induced variation in the medium of the compared sets of cultures. The inoculum from the sediment would carry over a much larger amount of extraneous materials that are incidentally carried down in the sediment. Certainly, more nonacid-fast organisms were inoculated onto these slants, as well as sufficient debris, to somewhat alter the pH of the medium. The amount carried over was of a much smaller volume and of a different character with the paraffin-ball inoculum. This difference in inocula probably plays some role in the present results, but did not exist in the cover-slip concentration method previously described. The variation in degree of cording in the colonies isolated from the surface as opposed to those from the bottom of the homogenized specimen was more marked on the cover-slip culture than that observed in the present study.

The possible significance of these observations must be considered. Even in the previously

untreated patient, the tubercle bacilli probably exist in variable forms, some of which are readily recognizable as the virulent *Mycobacterium tuberculosis* var. *hominis*, and others fit the description of avirulent acid-fast bacilli. The concept of environmental variants is not foreign in microbiology and may be the explanation for these findings. However, the recognition that variants can be obtained from the same clinical specimens seems important. In the small sample of 26 paired cultures, 9 (35 per cent) that were strongly corded on the PB-slants showed little or no cording on the S-slants. If only the sedimentation method had been used, the laboratory would have reported acid-fast bacilli of an avirulent nature. Such an interpretation would have been misleading to the clinician in that typical tubercle bacilli were isolated from the same aliquot of specimen by the hydrocarbon technique.

In reviewing the literature in mycobacteriology on concentration methods, hydrocarbon affinity, and the significance of cord factor, an explanation for some of the results can be postulated. Flotation techniques indicate that by increasing the specific gravity of an aqueous solution a large percentage of the tubercle bacilli present in the specimen can be floated. Conversely, if the specific gravity of the solution is reduced to 0.999, one can only sediment down by centrifugation about 20 per cent of the organisms (18). Silverstolpe (21) found that the specific gravity of the tubercle bacillus varied over a wide range—0.79 to 1.07—with a mean value just below 1.00. It is known that the tubercle bacillus is unusual in its high lipid content. There is ample evidence that the various species of mycobacteria contain variable amounts of cord factor (2, 4–14). Of these species, the virulent mammalian tubercle bacilli have been demonstrated to have the highest concentration of cord factor by both biochemical identification and by the morphologic manifestation, i.e., cording, of this substance. Cording appears to be the best single morphologic characteristic of virulence in the genus Mycobacterium. Koch in 1884 (49) originally described the corded growth of typical virulent tubercle bacilli. Middlebrook, Dubos, and Pierce in 1947 (2) first correlated the degree of cording with the degree of virulence. The work of both Pottenger (50), who noted the presence of "interbacillary wax" surrounding tubercle bacilli in fresh sputum specimens, and Hanks (51), who had demonstrated the presence of a capsule around tubercle bacilli in clinical material by means of negative "neutral-red" staining, support the premise that cord factor is naturally present surrounding virulent tubercle bacilli in the human host. Bloch in 1950 (3) extracted from the surface of virulent tubercle bacilli a lipid substance which was directly related to the cording seen microscopically. Cord factor has been identified by Noll (52) as trehalose 6,6′-dimycolate. Although the present writers do not know the specific gravity of cord factor, if it correlates with other paraffin-like substances, it may be around 0.800. The presence, absence, or intermediate amounts of cord factor on tubercle bacilli may account for the great variation in specific gravities. This is in agreement with the present findings that the more virulent bacilli (as manifested by tight cording) are repeatedly harvested from the surface of the supernatant fluids or the homogenized specimens.

The results of others (25, 26), indicating that lipophilia is a prominent characteristic of virulent acid-fast bacilli, are confirmed by the findings noted with the paraffin concentration technique. This characteristic also appears to be related to the surface coating of the organisms. The nonpolarity of this surface permits easier wetting of the organisms by substances which are also relatively nonpolar, such as the hydrocarbon group of compounds. This lipophilia can be affected in a number of ways. It can be decreased by removing the waxy coat (3, 50) by the action of certain surface active agents, e.g., Tween 80 (2, 6, 7, 48) and by coating the surface with substances present in immune serum (38). It can be increased by coating the bacilli with minute amounts of certain hydrocarbons. These known factors and probably some that are not yet realized undoubtedly were operative in the present study. This may account particularly for the less complete fractionation of virulent organisms by the paraffin method as opposed to the clear distinction evident by the siliconized cover-slip method.

The significant difference noted in the contamination rates by the two concentration methods is probably explained by the same mechanisms so far discussed, namely, the relative lack of lipophilia on the part of most bacteria and the probable greater specific gravity of most nonmycobacterial (and less lipid-containing) microorganisms.

Summary

A comparison of two concentration methods for acid-fast bacilli was made on 240 sputum specimens. From the same digested and homogenized aliquot of sputum a paraffin ball was used to concentrate the organisms from the surface, and the centrifuged sediment was used as a second concentrate.

One hundred of the specimens were positive for acid-fast bacilli. Ninety-five were *Mycobacterium sp.* and 5 were *Nocardia sp.* Of the specimens positive for mycobacteria, 73.7 per cent were positive by both methods; 92.6 per cent were positive by sedimentation concentration; and 81.0 per cent were positive by paraffin-surface concentration.

A significantly greater number of slants were contaminated by the sedimentation-concentration method (10.8 per cent) than by the paraffin method (1.25 per cent).

The paraffin-concentration method in a significant number of specimens (73 per cent) harvested a population of mycobacteria which, in primary isolation, possessed a greater degree of cording than the organisms harvested by the sedimentation method. In 35 per cent of these paired specimens, in which the cultures of the paraffin-ball-collected organisms were strongly corded, the corresponding cultures of the sediment-collected organisms were poorly corded or completely disoriented.

Although more organisms are collected by sedimentation, they are often of less virulent or avirulent types. Therefore, the interpretation of present routine laboratory reports may not represent the true bacteriologic status of the patient. The hydrocarbon-concentrating method was superior in concentrating the more virulent tubercle bacilli present in the specimens.

The concept of the presence of environmental and/or true variants of acid-fast bacilli within single sputum specimens is proposed. The correlation between virulence and lipophilia is supported by the findings in this study. The possible relationship of the amount of cord factor to the specific gravity of tubercle bacilli is postulated.

Sumario

Estudio Cultural de los Microbios Acidorresistentes Concentrados por las Técnicas de la Hidrocarburo-Adsorción y la Sedimentación

En 240 ejemplares de esputo, se hizo una comparación de dos técnicas de concentración para bacilos ácidorresistentes. Tomando la misma parte alícuota digerida y homogeneizada del esputo, se usó una bola de parafina para concentrar los microbios de la superficie, y el sedimento centrifugado como segundo concentrado.

Cien de los ejemplares resultaron positivos para bacilos ácidorresistentes, mostrando 90 *Mycobacterium sp.* y 5 *Nocardia sp.* De los ejemplares positivos para micobacterias, 73.7 por ciento fueron positivos con ambas técnicas; 92.6 por ciento resultaron positivos por la concentración con la sedimentación y 81.0 por ciento por la concentración superficial con parafina.

Un número (10.8 por ciento) significativamente mayor de siembras inclinadas se contaminó con el método de la concentración por sedimentación que con el método de la parafina (1.25 por ciento).

En una importante proporción de los ejemplares (73 por ciento), la técnica de la concentración por parafina produjo una población de micobacterias que, al ser aisladas por primera vez, poseían un acordonamiento mayor que las cultivadas por el método de la sedimentación. En 35 por ciento de estos ejemplares apareados, en los que los cultivos de los microbios recogidos con la bola de parafina mostraban cordones de nota, los cultivos correspondientes de los bacilos recogidos del sedimento mostraban cordones defectuosos o totalmente desorientados.

Aunque se obtienen más microbios con la sedimentación, son a menudo de formas menos virulentas o avirulentas. Por lo tanto, la interpretación de los actuales informes corrientes de laboratorio quizás no represente el verdadero estado bacteriológico del enfermo. La técnica de la concentración con hidrocarburo se mostró superior para concentrar los bacilos más virulentos que contenía el ejemplar.

Se propone el concepto de la presencia de variantes ambientales y/o verdaderas de bacilos ácidorresistentes en ciertos ejemplares de esputo. La correlación entre la virulencia y la lipofilia encuentra apoyo en los hallazgos de este estudio. Se presupone la posible relación de la proporción del factor cordón con la densidad de los bacilos tuberculosos.

Resume

Une étude de culture de micro-organismes acido-résistants concentrés par adsorption à l'hydrocarbone et par des méthodes de sédimentation

On a fait une comparaison entre deux méthodes de concentration pour bacilles acido-résistants, sur 240 échantillons d'expectoration. On utilisa pour la même fraction d'expectoration digérée et homogénéisée une boule de paraffine pour concentrer les organismes de la surface, et on utilisa le sédiment centrifugé comme second concentré.

Une centaine des échantillons fut positive pour bacilles acido-résistants. Quatre vingt quinze furent des *Mycobacterium sp.* et 5 furent *Nocardia sp.* Parmi les échantillons positifs pour mycobactéries, 73,7% furent positifs d'après les deux méthodes; 92,6% furent positifs avec la méthode de sédiment concentré, et 81,0% furent positifs avec la méthode de concentration par de la paraffine en surface.

Avec la méthode de sédiment concentré, il y eut une quantité de milieux contaminés nettement plus grande (10,8%) qu'avec la méthode à la paraffine (1,25%).

La méthode de concentration à la paraffine récolta, dans un nombre important d'échantillons (73%), une population de mycobactérium qui dès la première isolation possédait un degré de "corde" plus élevé que les organismes récoltés par la méthode de sédimentation. Dans 35% de ces échantillons groupés par paire, dans lesquels les cultures de germes récoltés à la boule de paraffine furent fortement "en corde," les cultures correspondantes de germes obtenus par sédimentation furent peu "cordées" ou complètement dispersées.

Bien que plus de germes aient été obtenus par sédimentation, ils furent souvent de moindre virulence ou de type avirulent. Par conséquent, l'interprétation des rapports de laboratoire d'après les techniques coutumières actuelles peuvent ne pas représenter le véritable état bactériologique du malade. La méthode de concentration à l'hydro-carbone fut supérieure pour concentrer les bacilles tuberculeux plus virulents présents dans les échantillons.

L'auteur propose le concept de la présence de variétés d'environnement, ou/et de variétés vraies de bacilles acido-résistants dans des échantillons uniques d'expectoration. Le rapport entre la virulence et la lipophilie est confirmé par les données de cette étude. La corrélation possible entre le taux de facteur "corde" et la gravité spécifique des bacilles tuberculeux est stipulée.

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REFERENCES

(1) Gray, J. B., Chodosh, S., and Reinisch, E.: A new, rapid concentration and differential culture technique for the Mycobacterium and Nocardia organisms, presented at the annual meeting of the American Trudeau (now Thoracic) Society, Chicago, May 24, 1959 (abstract printed in Amer Rev Tuberc, 1959, *79*, 831).

(2) Middlebrook, G., Dubos, R. J., and Pierce, C.: Virulence and morphological characteristics of mammalian tubercle bacilli, J Exp Med, 1947, *86*, 175.

(3) Bloch, H.: Studies on the virulence of tubercle bacilli: Isolation and biological properties of a constituent of virulent organisms, J Exp Med, 1950, *91*, 197.

(4) Yegian, D., and Kurung, J.: Growth pattern and virulence of tubercle bacilli, Amer Rev Tuberc, 1952, *65*, 181.

(5) Will, D. W., Bishop, F., Bogen, E., Djang, A. H. K., and Carpenter, C. M.: Comparative morphology of acid-fast bacilli, Dis Chest, 1951, *19*, 387.

(6) Melvin, I. G., and Vandiviere, H. M.: The titration of cord formation as related to virulence of mycobacteria, Amer Rev Tuberc, 1958, *78*, 83.

(7) Vandiviere, H. M., Melvin, I. G., and Kennedy, H. E.: Titration of cord formation as a measure of pathogenicity of wild-type acid-fast bacilli, typical and atypical, Amer Rev Tuberc, 1958, *78*, 799.

(8) Shepard, C. C.: Growth characteristics of tubercle bacilli and certain other mycobacteria in HeLa cells, J Exp Med, 1957, *105*, 39.

(9) Shepard, C. C.: Growth characteristics in HeLa cells of the rapidly growing acid-fast bacteria, *Mycobacterium fortuitum*, *M. phlei*, and *M. smegmatis*, J Bact, 1957, *73*, 722.

(10) Shepard, C. C.: A comparison of the growth of selected mycobacteria in HeLa, monkey kidney, and human amnion cells in tissue culture, J Exp Med, 1958, *107*, 237.

(11) Shepard, C. C.: Behavior of the "atypical" mycobacteria in HeLa cells, Amer Rev Tuberc, 1958, *77*, 968.

(12) Krasnow, I., Wayne, L. G., and Salkin, D.: A microcolonial test for the recognition of virulent mycobacteria, Amer Rev Tuberc, 1955, *71*, 361.

(13) Wayne, L. G., Krasnow, I., and Huppert, M.: Characterization of atypical mycobacteria and of Nocardia species isolated from clinical specimens: Characterization of atypical mycobacteria by means of the microcolonial test, Amer Rev Tuberc, 1957, *76*, 451.

(14) Huppert, M., Wayne, L. G., and Juarez, W. J.: Characterization of atypical mycobacteria and of Nocardia species isolated from clinical specimens: II. Procedure for differentiating between acid-fast microorganisms, Amer Rev Tuberc, 1957, *76*, 468.

(15) Richmond, L., and Cummings, M. M.: An evaluation of methods of testing virulence of acid-fast bacilli, Amer Rev Tuberc, 1950, *62*, 632.

(16) SUTER, W. E., AND DUBOS, R. J.: Variability of BCG strains (Bacillus Calmette-Guerin), J Exp Med., 1951, *93*, 559.

(17) KLEIN, G. C., MALTZ, M., CUMMINGS, M. M., AND FISH, C. H.: Efficacy of centrifugation as a method of concentrating tubercle bacilli, Amer J Clin Path, 1952, *22*, 581.

(18) ELLERMAN, V., AND ERLANDSEN, A.: Nachweis von Tuberkelbazillen im Sputum, Z Hyg Infektionskr, 1908, *61*, 219.

(19) PETROFF, S. A.: Some cultural studies on the tubercle bacillus, Bull Johns Hopkins Hosp, 1915, *26*, 276.

(20) BALDWIN, E. R., PETROFF, S. A., AND GARDNER, L. S.: Tuberculosis, Bacteriology, Pathology, and Laboratory Diagnosis, Lea & Febiger, Philadelphia, 1927, p. 237.

(21) SILVERSTOLPE, L.: Förbatträd Metod för Påvisande av Tuberkelbacterier, Nord Med, 1948, *40*, 2220.

(22) PETROFF, S. A.: A new and rapid method for the isolation and cultivation of tubercle bacilli directly from sputum and feces, J Exp Med, 1915, *21*, 38.

(23) FELSEN, J.: A method for detecting sparsely distributed tubercle bacilli, AMA Arch Path, 1930, *10*, 110.

(24) HANKS, J. H., CLARK, H. F., AND FELDMAN, H.: Concentration of tubercle bacilli from sputum by chemical flocculation methods, J Lab Clin Med, 1938, *23*, 736.

(25) REED, G. B., AND RICE, C. E.: The behavior of acid-fast bacteria in oil and water systems, J Bact, 1931, *22*, 239.

(26) WAYNE, L. G., AND JUAREZ, W. J.: A solvent partition technique for taxonomic differentiation within the genus Mycobacterium, Bact Proc, 1955, *108*, 1955.

(27) NAGY, A. H.: Evaluation of the tubercle bacillus concentration methods of Petroff, Pottenger and chemical flocculation, J Lab Clin Med, 1939, *25*, 67.

(28) COURATTE - ARNAUDE (1903): Quoted by Hawirko and Murray in reference 39.

(29) BERNHARDT, G.: Über die Verwendung von Antiformin und Ligroin für den Nachweis der Tuberkelbazillen im Sputum, Deutsch Med Wschr, 1909, *35*, 1428.

(30) HASERODT, H.: Neue Methoden zum Nachweis von Tuberkelbacillen im Sputum, Hyg Rundschau, 1909, *19*, 699.

(31) UHLENHUTH, P., AND XYLANDER: Antiformin ein bakterienauflösendes Desinfektionsmittel, Berl Klin Wschr, 1908, *45*, 1346.

(32) KINYOUN, J. J.: Note on Uhlenhuth's method for sputum examination for tubercle bacilli, Amer J Public Health, 1915, *5*, 867.

(33) KRAUSS, W., AND FLEMING, J. S.: A simple method of concentrating tubercle bacilli in sputum and urine, J Lab Clin Med, 1915–1916, *1*, 919.

(34) POTTENGER, J. J.: The demonstration of rare tubercle bacilli in sputum, Amer Rev Tuberc, 1931, *24*, 583.

(35) ANDRUS, P. M., AND MACMAHON, H. E.: The use of volatile hydrocarbons in the concentration of tubercle bacilli, Amer Rev Tuberc, 1924, *9*, 99.

(36) MUDD, S., AND MUDD, E. B. H.: On the surface composition of normal and sensitized mammalian blood cells, J Exp Med, 1926, *43*, 127.

(37) MUDD, S., AND MUDD, E. B. H.: The surface composition of the tubercle bacillus and other acid-fast bacteria, J Exp Med, 1927, *46*, 167.

(38) MUDD, S., AND MUDD, E. B. H.: On the mechanism of the serum sensitization of acid-fast bacteria, J Exp Med, 1927, *46*, 173.

(39) HAWIRKO, R. Z., AND MURRAY, E. G. D.: Oil partition for the collection of small numbers of tubercle bacilli from aqueous suspensions, Canad J Public Health, 1954, *45*, 208.

(40) CROWLE, A. J.: Filtration of mycobacteria from organic solvents, Amer Rev Tuberc., 1958, *77*, 290.

(41) RAHN, O.: Ein Paraffin Zersetzender Schimmelpilz, Zbl Bakt, 1906, *16*, 382.

(42) SÖHNGEN, N. L.: Benzin, Petroleum, Paraffinöl und Paraffin als Kohlenstoff- und Energiequelle für Mikroben, Zbl Bakt, 1913, *37*, 595.

(43) BÜTTNER, H.: Zur Kenntnis der Mykobakterien insbesondere ihres Quantitativen Stoffwechsels auf Paraffinnährböden, Arch Hyg Bakt, 1926, *97*, 12.

(44) FREY, C. A.: A method for detecting acid-fast bacteria in the soil, Science, 1930, *71*, 366.

(45) FREY, C. A., AND HAGAN, W. A.: The distribution of acid-fast bacteria in soils, J. Infect Dis, 1931, *49*, 497.

(46) GORDON, R. E., AND HAGAN, W. A.: A study of some acid-fast actinomycetes from soil with special reference to pathogenicity for animals, J Infect Dis, 1936, *58*, 200.

(47) GRAY, J. B.: Unpublished data.

(48) FISHER, M. W.: The growth of tubercle bacilli in silicone-coated glass tubes, J Bact, 1954, *67*, 613.

(49) KOCH, R.: Die Aetiologie der Tuberkulose, Mitt Gsndhtsamte, 1884, *2*, 1.

(50) POTTENGER, J. E.: Clinical Tuberculosis, ed 1, C. V. Mosby Co., St. Louis, 1917, p. 548.

(51) HANKS, J. H.: Personal communication, 1959.

(52) NOLL, H.: Chemistry of cord factor, a toxic glycolipid of *M. tuberculosis*, Advance Tuberc Res, 1956, *7*, 149.

STUDY OF LUNG SPECIMENS PREPARED BY FUME FIXATION[1]

ELISE JONES

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Introduction

Fifteen whole lungs, taken from autopsy cases in which clinical history and gross examination gave no evidence of pathologic change other than occasional minimal pulmonary edema, were prepared by a method of fume fixation. This was undertaken because of dissatisfaction with distortion by present methods of fixation and preparation.

Method and Material

Each fresh lung was suspended (individually) on a glass tube by tying and suturing the main stem bronchus around the tube which was connected with separate containers of 50 per cent formalin and 50 per cent ethyl alcohol; these fixative solutions were, in turn, connected with a supply of forced air. The lung was suspended in a hood from which fumes and microorganisms (if present) were prevented from entering the room in significant amounts.

Specimens used were taken from the body, and within one hour were affixed to the apparatus. Either the right or left lung was used in each case (never both), being severed at the hilum with as long a segment of main stem bronchus as it was feasible to obtain. Weights of these specimens ranged from 280 to 520 gm. Microscopic sections were impregnated with paraffin and stained with hematoxylin and eosin in the usual manner. These sections were cut from anterior and posterior regions of all lobes and labeled accordingly.

Results

The results of the study are set forth in tables 1, 2, and 3.

Discussion

Various air pressures and times were used, ranging from 3/16 to 1 pound, and 3.7 to 6.0 days. There was difficulty in maintaining stable pressure because of porosity of visceral pleura not in a negative pressure, as in the thoracic cavity. It was found that overdistention of alveolar spaces must be produced in order to obtain good fixation in all areas. This resulted in a lung grossly appearing, as seen in a maximal or superinspiratory state (figures 1 and 2). Optimal pressure for satisfying these conditions was found to be one-half pound for the first eighteen to twenty-four hours, then allowing pressure to fall to one-third or one-fourth pound for the remainder of the total time of four to six days. The two lungs that are classed as excellent (table 1) were treated with 1-pound pressure × 20 hours, then 0.68 pounds pressure × 3.7 days; and one-half pound pressure × 18 hours, and 3/16 pounds pressure × 78 hours. All results were classified immediately and, when the gross evaluation was rechecked a week or two later, the result was considered to be somewhat improved due to complete drying of unfixed areas. Results were classified and recorded, however, on original inspection.

Alveolar dilatation was noted microscopically in all sections of all specimens with occasional ruptured alveolar walls (figure 3). This was interpreted as artificially produced emphysema, and was present regardless of the amount of air pressure used. One lung contained emphysematous blebs which were noted on gross inspection of the fresh specimen; these areas fixed beautifully by fume fixation and remained nonfragile on sectioning, resulting in a clear-cut demonstration of the anatomic structure of this change (figure 4). Lungs containing edema on external gross inspection and palpation of the fresh specimen were poorly fixed or unfixed in these areas (figures 5–7).

Results in this series compared favorably with those of Blumenthal and Boren (1), whose work was published during the time when the studies were being done in this laboratory. They encountered similar problems of unstable air pressure and unfixed areas. The method of microscopic slide preparation used in their work was not the method used routinely in most laboratories, as was done in this study.

[1] From the Institute of Pathology, University of Tennessee, Memphis; and Oakville Memorial Sanatorium, Oakville, Tennessee.

TABLE 1

CLASSIFICATION OF GROSS RESULTS

	Color	Dry	Fragile	Weight on Handling	Unfixed Areas
Excellent	Normal	Yes	No	Light	No
Good	Normal or slightly darker	Yes	No	Light	No
Fair	Dark brown	Yes	No	Moderately light	Some
Poor	Black	Focal wet areas	No	Slightly heavy	Many

TABLE 2

CLASSIFICATION OF MICROSCOPIC RESULTS

	Fixation	Artificial Emphysema	Unfixed Areas
Excellent	Excellent	Some	No
Good	Good	Some	No
Fair	Fair	Yes	Yes (few)
Poor	Poor to unfixed	Yes	Many and massive

TABLE 3

EVALUATION OF 15 GROSS AND MICROSCOPIC SPECIMENS PREPARED BY FUME FIXATION

Fixation	Gross	Microscopic
Excellent	2	2
Good	3	3
Fair	4	3
Poor	6	7

Note: Close correlation was obtained in the individual specimens.

SUMMARY

Fifteen lungs were prepared by fume fixation with alcohol and formalin. The results were unpredictable, but depended mainly on air pressure level and duration of fixation. The chief problems encountered were inability to maintain stable air pressure due to loss of air through visceral pleura when the lung is outside the thorax, areas left unfixed, and overdistention with production of artificial emphysema.

This method appears to be impracticable for routine use in surgical or autopsy pathology because of the time required and the unreliability of the results. It is not believed amenable for study and diagnosis of lungs containing destructive and fibrotic disease processes because such changes would tend to inhibit diffusion of fumes of the fixatives. Its chief use appears to be in production of beautiful specimens for demonstrations and study.

SUMARIO

Estudio de los Ejemplares Pulmonares Preparados por la Fijación Fumeante

Quince pulmones fueron preparados por la fijación fumeante con alcohol y formalina. Los resultados fueron impredecibles, pero dependieron principalmente del nivel de la presión aérea y la duración de la fijación. Los mayores problemas encontrados fueron la incapacidad para mantener una presión aérea estable debido a la pérdida de aire a través de la pleura visceral cuando el pulmón está fuera del tórax, las zonas dejadas sin fijas y la hiperdistensión con producción de enfisema artificial.

Este método parece ser impracticable para empleo sistemático en la histopatología quirúrgica o autópsica, debido al tiempo que consume y a la inseguridad de los resultados. No parece ser utilizable para el estudio y diagnóstico de los pulmones que contienen procesos patológicos destructores y fibrosos por tender estas alteraciones a inhibir la difusión de los vapores de los fijadores. Su principal aplicación parece quedar en la producción de bellos ejemplares para demostraciones y estudio.

RESUME

Etude de pièces de poumon préparées par fixation à la vapeur

Quinze poumons ont été préparés par fixation à la vapeur, avec de l'alcool et du formol. Les résultats furent imprévisibles, mais dépendirent principalement du niveau de pression de l'air et de la durée de la fixation. Les principaux problèmes rencontrés furent l'impossibilité de maintenir une pression d'air stable à cause de la déperdition d'air à travers la plèvre viscérale, quand le poumon est en dehors du thorax, régions qui restant non fixées, et une surdistension avec production d'un emphysème artificiel.

Cette méthode semble être impraticable pour un

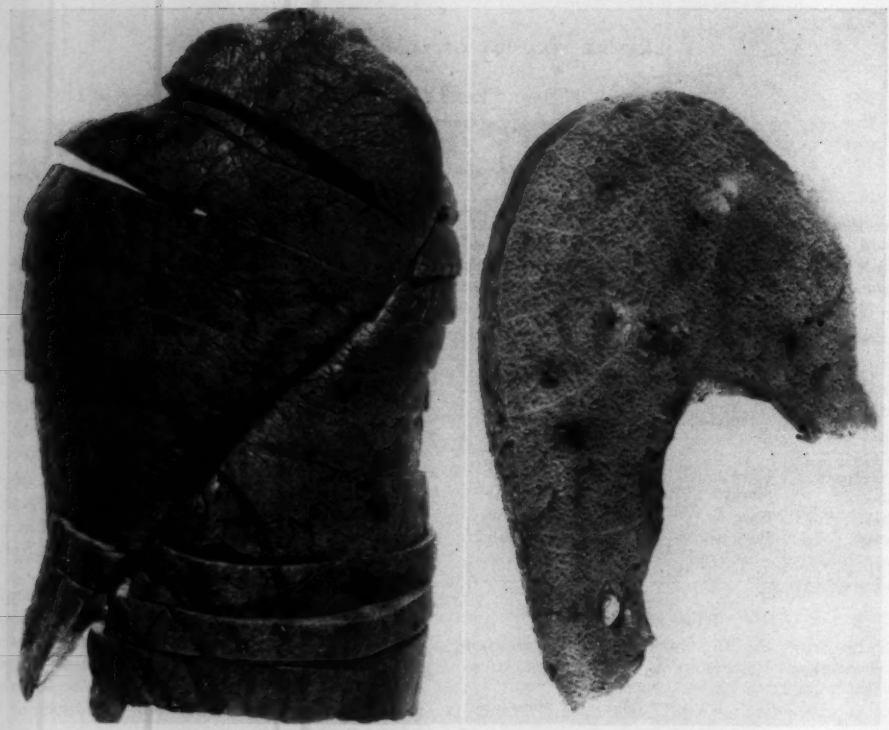

FIG. 1 (Left). Gross specimen classed as excellent is in a state of moderate overdistention.
FIG. 2 (Right). Cut section of specimen in figure 1.

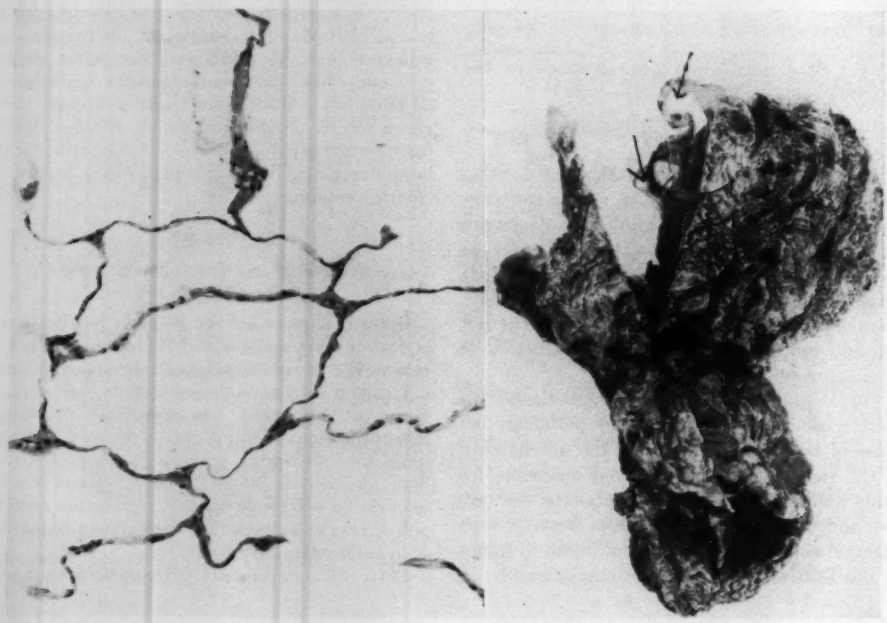

FIG. 3 (Left). Photomicrograph of specimen in figure 1 includes the excellent fixation obtained, as well as overdistended alveoli and ruptured alveolar walls.

FIG. 4 (Right). This specimen in the fresh state contained emphysematous blebs (arrows) which fixed well by the fume fixation method.

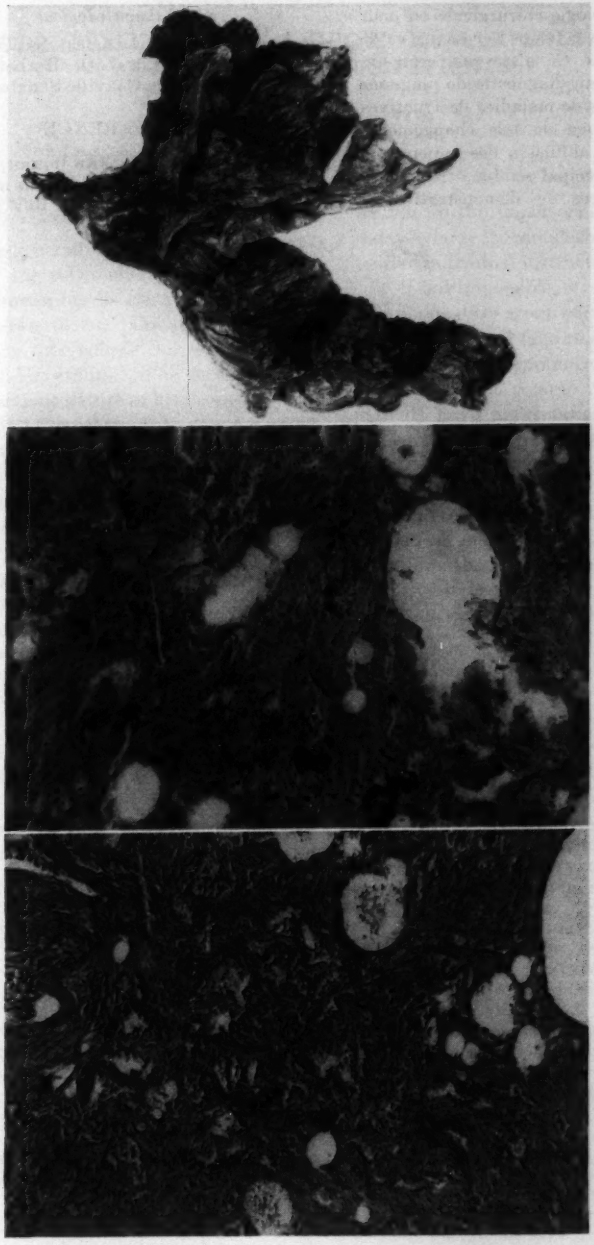

FIG. 5 (Left). Photomicrograph of an area of poor fixation in specimen containing edema.
FIG. 6 (Center). Illustrates focal areas of poor fixation.
FIG. 7 (Right). Gross specimen classed as "poor."

usage courant en pathologie chirurgicale ou pour les autopsies en raison du temps nécessaire et de l'infidèlité des résultats. Ce n'est pas, croit-on, applicable à l'étude et au diagnostic de poumons contenant des processus de maladies destructives et fibrotiques, parce que de tels changements tendraient à inhiber la diffusion des vapeurs de fixatifs. Son emploi principal semble être la production de belles pièces de démonstration et d'étude.

Acknowledgment

Appreciation for technical assistance is expressed to Miss Elizabeth Herbers and Miss Maggie Wingo of the Oakville Sanatorium.

REFERENCE

(1) Blumenthal, B. J., and Boren, H. G.: Lung structure in three dimensions after inflation and fume fixation, Amer Rev Tuberc, 1959, *79*, 764.

AN OBJECTIVE EVALUATION OF A GROUP HEALTH EDUCATION PROGRAM FOR TUBERCULOUS PATIENTS[1,2]

ALBERT J. STRATTON, JR.[3]

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INTRODUCTION

Today, it is generally acknowledged that there is a need for the tuberculous patient to understand the nature of his disease and its treatment. It is well known that a patient's ignorance of facts about his tuberculosis can produce unfortunate results. For example, if he does not understand the infectious nature of his disease, he may be careless and infect others. If he does not understand the nature of treatment procedures, he may not cooperate sufficiently to permit their application. Any misunderstanding of words and concepts regarding tuberculosis may contribute to a patient's anxiety by leaving him with a feeling of uncertainty as to his condition, and thus impede his recovery.

Most authorities agree on the importance of a patient's knowing about his disease. The need for good instruction is evident. However, authorities differ as to how the patient can be best educated.

Coleman, Hurst, and Hornbein (1) state that only individual instruction of the patient by his physician is of value; they believe that group procedures could be detrimental, for they tend to disrupt the patient-physician relationship. They stress the role of emotional blocking in preventing a tuberculous patient from learning and accepting the facts of his illness. They believe that only the patient who individually "works through" his "blocks" can eventually learn about his disease.

Wandelt (2), Kendig (3), Vernier (4), and others believe there is a need for formal group education to teach the patient about tuberculosis. They argue that the change from the intimate, small private or semi-private sanatorium of yesteryear to the impersonality and complexity of today's large tuberculosis hospital renders extensive individual instruction of the patient difficult, if not impossible.

Proponents of group education generally do not believe emotional factors are the primary reason for the patient's ignorance of his disease. Rather, they think that a large number of tuberculous patients have never been exposed to the basic facts of anatomy, physiology, and hygiene; therefore, they cannot be expected to know these facts.

Considering these two schools of thought on the value of group education procedures, an objective evaluation of the problem would be helpful. Therefore, the present study attempts to answer objectively the question: "Is a group health education program of value to tuberculous patients?"

METHOD

To determine the feasibility of developing instruments which would be suitable for such an evaluation, a number of preliminary studies were conducted. One study dealt with the validation of a short nonverbal intelligence test (5) for use with illiterate patients. Another study attempted to develop an index of denial of illness by the use of a "selective memory technique." This technique did not show promise and was not used in the final investigation.

As there were no adequate instruments available for an objective evaluation of patients' knowledge of tuberculosis, new tests were designed to measure a wide range of general information about the disease.

A tuberculosis vocabulary test was devised. This test consisted of forty words commonly used by the hospital personnel: for example, *sputum*, *contagious*, and *fluoroscopy*. Responses were graded qualitatively on a three-point scale (two-one-zero). The total score consisted of the number of words the patient knew. There was no penalty for awkwardness of expression, and any definition nearing the true meaning of a word was accepted. When the patient demonstrated that he knew what a word meant, he was credited with a passing definition. Most of the words on the list were scored (either right or wrong) but, to help in scoring marginal responses, a list of criteria was

[1] Based on research conducted in partial fulfillment of the requirement for the degree of Doctor of Philosophy of Western Reserve University.

[2] Research conducted at Sunny Acres, Cuyahoga County Tuberculosis Hospital, Cleveland, Ohio.

[3] Present address: Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, Pennsylvania.

developed. The reader familiar with the Wechsler Adult Intelligence Scale (6) will appreciate the simplicity and objectivity with which such items can be scored.

To measure the more over-all aspects of the patients' understanding of tuberculosis, a comprehension test was developed. The questions were aimed at tapping the patients' knowledge of the cause of the disease, how it is transmitted, the need for precautionary measures, the disease process, and the reasons for treatment procedures. For example, the first question asks: "What causes tuberculosis?" This test was also graded qualitatively on a three-point scale. To help scoring marginal responses, criteria were developed for each scoring level.

During the investigation it became apparent that a new and "visual" approach was needed to objectively evaluate the patients' concept of the lungs. For this purpose, a "draw-the-lungs test" was devised. The patient in this test is presented a blank outline of the human figure, and he is requested to draw in the lungs. The outline of the human figure was adapted from the diagram presented by Kimber, Gray, and Stackpole in *Textbook of Anatomy and Physiology* (7). The drawings were rated as to size, shape, and location by two tuberculosis physicians. High reliability (rho 0.95) was found between the ratings.

Only one test was available which presented norms from other tuberculosis hospitals. This was Newman's questionnaire, "What do you know about tuberculosis?" (8). Therefore, this test was included in the present study.

To evaluate changes in anxiety level that might be effected by a group education program, the Taylor Manifest Anxiety Scale (9) was given. This scale is a psychometric instrument designed to measure manifest anxiety reactions. The scale consists of simple statements such as, "I cannot keep my mind on one thing," "At times I lose sleep over worry." The patient answers "true," or "false."

An adaptation of the Madison Sentence Completion Form (10) was used to evaluate the patients' attitudes toward tuberculosis. The sentence completion method is a projective technique which is widely used by clinical psychologists. It consists of a number of incomplete sentences presented to the patient for completion. For example: "While I am here ————————," or "The future looks ————————." It has been found that by completing these sentences the patient often expresses his own wishes, desires, fears, likes, and dislikes. Calden (10) devised the Madison Sentence Completion Form specifically to evaluate the attitudes and emotional reactions of tuberculous patients. A preliminary study with this scale indicated that responses to many of the items could be easily rated as "favorable" or "unfavorable." The two categories were assigned quantitative values to permit statistical treatment.

A "denial scale" was developed in an attempt to determine the degree to which a patient emotionally rejects knowledge of his disease. The items on this scale were based on statements expressed by patients who manifested clinical symptoms of denial. Other statements were suggested by the literature dealing with denial of illness. The final selection of items for the scale was made with the help of the hospital's consulting psychiatrist and the Social Service staff.

The patient was presented statements such as, "I don't believe that my tuberculosis is as serious as they say," and "The doctor's orders are more strict than need be for my case." He was asked whether he *agreed completely*, *agreed to some extent*, or *disagreed* with the statement. The three categories also were assigned quantitative values to permit statistical treatment.

Information as to the patient's name, sex, race, religion, age, birthplace, marital status, occupation, and years of formal schooling was obtained from Social Service records.

The investigator interviewed each patient for approximately one hour. Testing sessions prior to the group program lasted two weeks. Pre-testing was completed four days before the first session of the program.

After the initial interview, the patients attended four lectures presented by the assistant medical director of Sunny Acres Hospital.

The lectures covered the cause and diagnosis of tuberculosis, the anatomy and physiology of the lungs, treatment procedures, and rehabilitation. Two films dealing with tuberculosis were shown. Discussion periods were held following the lectures.

The patients were retested at the completion of the program. Retesting started four days after the last group session. The post-program interviews were completed in two weeks.

The following statistical procedures were used to analyze data:

1. The investigator determined the mean score and standard deviation (from the mean) of each measure used in the study: vocabulary, comprehension, information, draw-the-lung test, sentence completion, and the denial scale. This included both the pre-program tests and post-program tests.
2. The differences between the pre-program and post-program scores of each of the above tests were obtained.
3. The t test, used to determine statistical significance, was applied to the difference in the means of each of the measures.
4. The Pearson Product Moment Correlation, to show relationship, was determined between intelligence quotient, years-of-formal-schooling, length-of-hospitalization, and the pre-program scores on the tuberculosis knowledge tests.

The subjects used in the study were selected according to set criteria. The patients were required to be first-admission cases of tuberculosis, and acute symptoms of the disease must have subsided. Sixty-five patients were available under

these criteria, and they were administered the pre-program tests. Fifteen patients were unavailable for post-program tests because they were unable to attend all four lectures. The final sample, therefore, includes the 50 patients who attended all four lectures.

Description of Sample

Number: 50 patients
First admissions
Sex: males—26, females—24
Average (mean) age, 34.5 years; range, 17 to 55 years
Race: Negro—28; white—22
Intelligence: mean I.Q.—91.5 (standard deviation—18.4); range: 60–135
Education: mean—8.9 years (standard deviation—3.4)
Marital status: married—32; single—18
Length of hospitalization: mean—120 days (standard deviation—78 days)
Occupations: unskilled—11; semi-skilled—12; skilled—6; professional—2; students—4; housewives—10

It should be noted that most of the patients belonged to the laboring class, and both the intelligence and educational levels of the sample were below average (the census report for 1957 states the national average for years of completed schooling is 11.8).

Results

The post-program testing revealed highly significant gains in the scores on all four tuberculosis knowledge tests (table 1). There was also a statistically significant decrease in the patients' anxiety level as measured by the Taylor Manifest Anxiety Scale.

Although the scores on the denial scale were lower following the program, the difference was not statistically significant.

The patients were found to have very favorable attitudes toward the hospital and treatment before the group program, and there was no appreciable change after the program.

TABLE 1

MEAN SCORES OF KNOWLEDGE TESTS (PRE-PROGRAM AND POST-PROGRAM)

Test	Pre-Program	Post-Program	Difference	t Test
Vocabulary	40.96	58.44	17.42	15.3*
Comprehension	15.98	20.82	4.84	10.9*
Information	18.28	19.70	1.42	5.35*
Lung drawings	62.99	38.04	−24.95†	8.53*

* Significant at the one per cent level of confidence.

† The lowered rank-score on the post-program lung-drawing test indicates improvement.

TABLE 2

RELATIONSHIP OF INTELLIGENCE, EDUCATION, AND LENGTH OF HOSPITALIZATION TO TUBERCULOSIS KNOWLEDGE TESTS (PRE-PROGRAM)*

	Intelligence Quotient	Formal Schooling	Length of Hospitalization
Vocabulary	0.66†	0.68	0.31
Comprehension	0.50	0.59	0.18
Information	0.57	0.65	−0.43
Lung drawings	0.45	0.39	0.65

* Significance of Pearson Product Moment correlation coefficient determined by t test

† Perfect positive relationship, r + 1.00; perfect negative relationship, r − 1.00

As predicted, a positive relationship was found between intelligence, years of formal schooling, and scores on the tuberculosis knowledge tests (table 2). Low relationship was found between length of hospitalization and scores on the pre-program knowledge tests, with one exception. A high correlation was found between length of hospitalization and score on the draw-the-lungs test. Possibly this is due to the greater opportunity of the longer-hospitalized patients to have seen pictures and roentgenograms of the lungs. This apparent retention of visual memories may have implications for health education programs.

There was a very significant improvement in the patients' concept of the lungs. Most striking was the pre-program concept of lung size: most patients believed that their lungs were considerably smaller than the actual size. After the lectures, they realized that a person has considerable lung tissue to spare. This realization may have been an important factor in the subsequent reduction of their anxiety.

Discussion

Judging from post-program interviews, the lectures were successful in that they gave the patient a feeling of satisfaction because he knew the staff was interested in him. The program answered some of his doubts about tuberculosis and gave him a feeling of hopefulness. It assured him that the hospital was up-to-date on treatment methods. And finally, the lectures gave him a feeling of knowing what was going to happen during the course of treatment.

In conclusion, this investigation shows that it

is possible to develop instruments to test a patient's knowledge of tuberculosis. The study also shows that it is possible to use these instruments for evaluating a group health education program.

The group program evaluation indicates that a patient with tuberculosis (a serious, chronic disease) can gain significant knowledge about his disease from group instruction. This is true even for a patient of relatively low intelligence and education. The study also shows that a group program is of therapeutic value in that it lessens patients' anxiety.

Summary

An objective evaluation of a group health education program for tuberculous patients was the purpose of this study. New tests were developed to measure a wide range of patients' general information about tuberculosis. These tests, as well as measures of attitude, anxiety, and denial of illness, were administered to 50 patients.

The patients attended four sessions. Lectures covered the cause and diagnosis of tuberculosis, the anatomy and physiology of the lungs, treatment procedures, and rehabilitation. Two films dealing with tuberculosis were shown. Discussion periods followed each lecture. The patients were retested at the completion of the program. The post-program testing revealed highly significant increases in knowledge about tuberculosis on all tests. There was a statistically significant decrease in patients' manifest anxiety level.

Sumario

Justipreciación Objetiva de un Plan de Enseñanza Sanitaria Colectiva para los Tuberculosos

Tiene por fin este estudio hacer una justipreciación objetiva de un plan de enseñanza sanitaria colectiva para tuberculosos. Se elaboraron nuevas pruebas para medir en amplia escala la información general que poseían los enfermos acerca de la tuberculosis. Dichas pruebas, así como mediciones de la actitud, la ansiedad y negación de la dolencia, se aplicaron a 50 enfermos.

Los enfermos asistieron a cuatro sesiones. Las conferencias abarcaron la causa y el diagnóstico de la tuberculosis, la anatomía y fisiología de los pulmones, los procedimientos terapéuticos y la rehabilitación. Se exhibieron dos películas dedicadas a la tuberculosis. Hubo períodos de discusión después de cada conferencia.

Al terminar las tareas, se recomprobó a los enfermos. Esta recomprobación reveló en todas las pruebas aumentos sumamente importantes en el conocimiento de la tuberculosis. Hubo una disminución estadísticamente significativa en el nivel de ansiedad manifiesta de los enfermos.

Resume

Une évaluation objective d'un programme d'éducation par groupe, portant sur l'hygiène, destiné aux malades tuberculeux

Le but de cette étude est une évaluation objective d'un programme d'éducation d'hygiène, par groupe, pour des malades tuberculeux. De nouveaux tests ont été mis au point pour mesurer l'information générale d'un large groupe de malades, au sujet de la tuberculose. Ces tests furent appliqués à 50 malades en même temps que des mesures de leur attitude, de leur anxiété, de leur négation de la maladie.

Les malades assistèrent à quatre séances. Des cours couvrirent la cause et le diagnostic de la tuberculose, l'anatomie et la physiologie des poumons, les moyens de traitement et la réhabilitation. Deux films concernant la tuberculose furent projetés. Des moments de discussion suivirent chaque cours.

Les malades furent retestés à la fin du programme. Les résultats des tests après ce programme montrèrent des gains tout à fait remarquables dans la connaissance de la tuberculose, dans tous les tests. On nota une diminution statistiquement remarquable dans les manifestations de type anxieux des malades.

REFERENCES

(1) Coleman, J. U., Hurst, A., and Hornbein, R.: Psychiatric contribution to care of tuberculosis patients, JAMA, 1947, *135*, 699.

(2) Wandelt, M.: A Planned Program of Education versus Incidental Instruction for Patients in Tuberculosis Therapy, unpublished Ph.D. dissertation, University of Michigan, 1954.

(3) Kendig, J. V.: Irregular discharge and patient education, in *Personality, Stress and Tuberculosis*, edited by P. J. Sparer, International University Press, Inc., New York, 1956, p. 459.

(4) Vernier, C. M.: The Baltimore V.A. Hospital Patient Education Program, unpublished paper received from author, October, 1957.

(5) McMurry, R., and King, J.: S R A Non-Verbal Form (Test), Science Research Associates, Chicago, 1947.

(6) Wechsler, D.: Manual for the Wechsler Adult Intelligence Scale, The Psychological Corporation, New York, 1955.

(7) Kimber, D., Gray, C., and Stockpole, C.: Textbook of Anatomy and Physiology, ed. 11, MacMillan, New York, 1946, p. 7.

(8) Newman, J.: What Do You Know About Tuberculosis? (Questionnaire), National Tuberculosis Association, New York, 1945.

(9) Taylor J.: A personality scale of manifest anxiety, J Abnorm Soc Psychol, 1953, *48*, 285.

(10) Calden, G.: A method for evaluating the attitudes of tuberculous patients, Amer Rev Tuberc, 1953, *67*, 722.

Case Reports

EXTRATHORACIC EGG-SHELL CALCIFICATIONS IN SILICOSIS[1]

ABRAHAM A. POLACHEK AND WALTER J. PIJANOWSKI

(Received for publication April 13, 1960)

Introduction

Egg-shell calcification of pulmonary or mediastinal lymph nodes has been reported in 20 to 40 per cent of patients with silicosis (1–3), and is generally considered characteristic of this entity (3–5). Although other writers (6) have thought that superimposed tuberculosis was the cause, there is no good evidence for this concept. Usually, in tuberculosis, the mulberry rather than the egg-shell type of calcification of lymph nodes is found.

Extrathoracic egg-shell calcification of lymph nodes has rarely been reported. Riemer (7) noted a case of silicosis with this type of calcification in a subdiaphragmatic pre-aortic lymph node. Grayson and Blumenfeld (3) mentioned one patient with similarly calcified abdominal lymph nodes who died of adenocarcinoma of the cecum with metastases and another patient with such involvement of a supraclavicular node. Jacobs and associates (2) report an interesting case of large intra-abdominal egg-shell calcifications due to silicosis.

The following two additional patients are presented and the probable pathogenesis of this unusual entity is discussed.

Case Reports

Case 1. S.J.M. was a 61-year-old white male who developed paralysis of the right upper extremity in July, 1957. He had a Jacksonian convulsion of the right upper extremity in November, 1957, and was hospitalized elsewhere. A pneumoencephalogram, an arteriogram, and a left frontotemporal trephine were performed on December 3, 1957, without establishing a definite diagnosis. Because of recurrence of convulsions, the patient was admitted to the hospital on January 14, 1958. The occupational history revealed that the patient had worked as a sandblaster for five years in the 1930's.

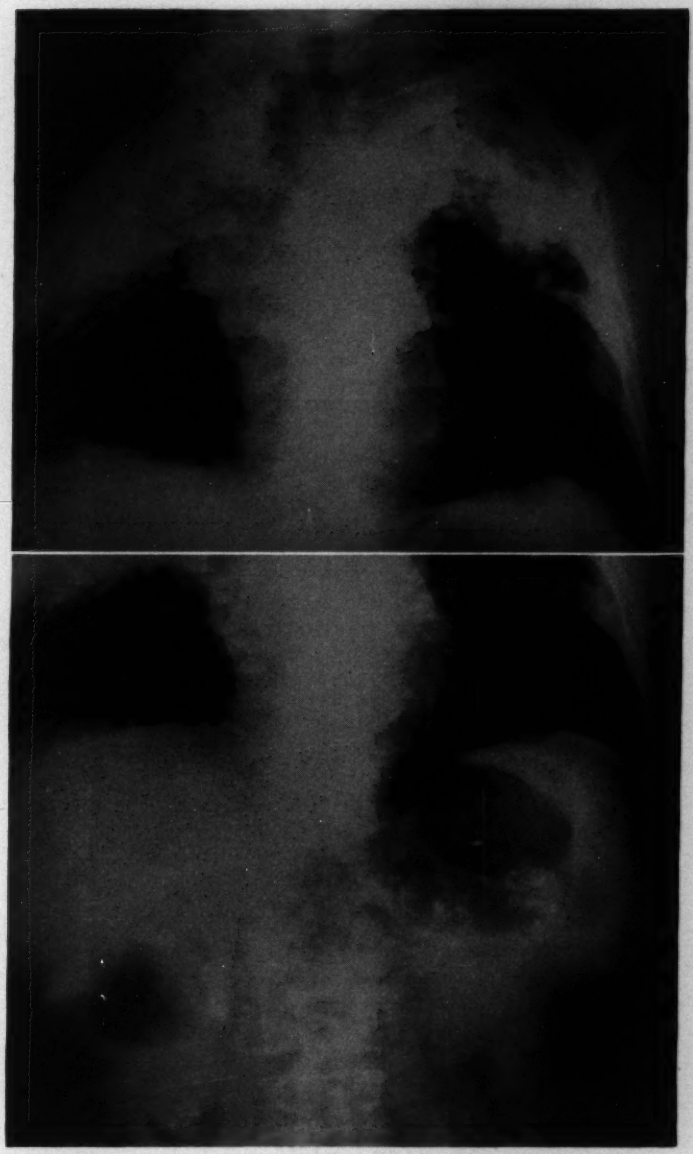
He was aphasic but able to respond to some questions. The temperature was 100° F.; pulse, 100 per minute; respirations, 22 per minute; and blood pressure 100 systolic, 60 diastolic in mm. of mercury. There was a scar over the left frontotemporal area with an underlying area of depression. A firm lymph node was palpable in the right supraclavicular region. The anteroposterior diameter of the chest was increased, and both lung fields were hyper-resonant. The heart sounds were distant and the second pulmonic sound was louder than the aortic. Spastic paralysis was found on the right side.

Laboratory studies, including cerebrospinal fluid, were normal. Sputum and gastric cultures were negative for tubercle bacilli and fungi. The chest roentgenogram (figure 1) showed bilateral opacification of the entire upper lung fields with numerous nodular densities, many with striking egg-shell calcifications measuring 2 to 3 cm. in diameter. A roentgenogram of the abdomen (figure 2) disclosed similar egg-shell calcific densities extending down to the level of L3. In the region of the spleen, multiple calcific densities 1 to 2 mm. in diameter were visualized. An electrocardiogram had changes consistent with pulmonary emphysema.

The patient improved in the first few days and regained his ability to speak. During the hospitalization, he had several episodes of dyspnea, cyanosis, and fever. The histoplasmin (1:100) skin reaction was negative. The reaction to tuberculin, first-strength PPD (0.00002 mg.), was negative; the reaction to intermediate strength PPD (0.0001 mg.) was positive. Biopsy of the right supraclavicular lymph node, measuring 2.5 cm. in diameter, showed a thickened calcified outer shell, with grayish-black contents. Microscopic examination (figure 3) revealed diffuse anthracotic pigmentation, hyalinization, and calcification consistent with silicosis. The patient had a stormy course, became severely dyspneic and cyanotic, went into shock, and died on May 16, 1958.

Post-mortem examination disclosed a markedly thickened pleura over the apices, with both lungs distended, firm, and stony to palpation because of calcification. The upper lobes showed broad interstitial whitish-gray scarring. The peribronchial, cervical, mediastinal, and abdominal lymph nodes (figure 4), including peripancreatic, peri-aortic, and hepatic nodes, were enlarged and hard, with calcifications of egg-shell type. Histologically the findings were identical with those of the previously described supraclavicular node. The spleen

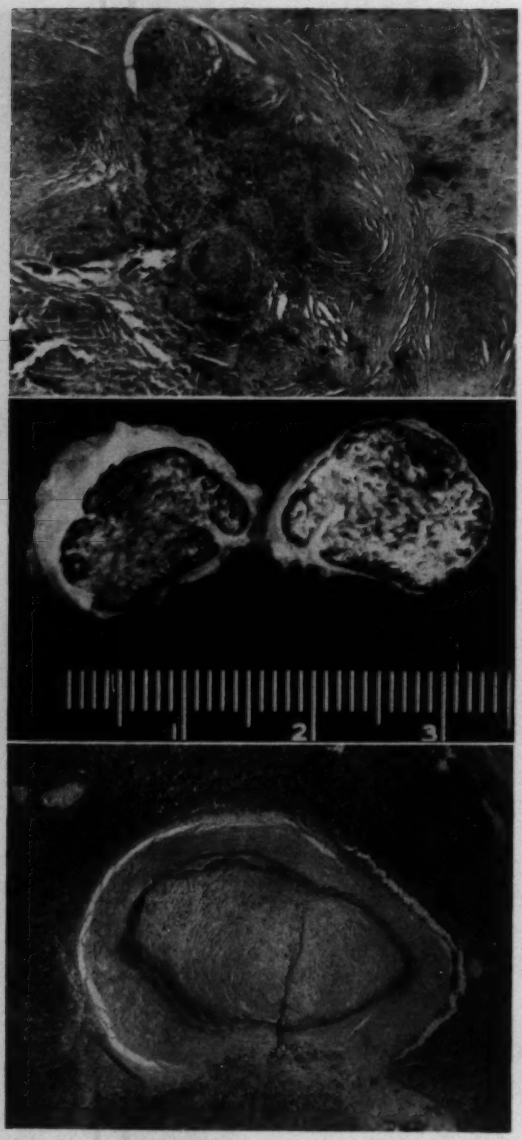
[1] From the Medical Service, Veterans Administration Hospital, Baltimore, Maryland, Fort Howard Division.



Case 1 (S.J.M.)

FIG. 1. (Upper). Chest roentgenogram with egg-shell calcifications of pulmonary and right supraclavicular lymph nodes.

FIG. 2 (Lower). Abdominal roentgenogram with egg-shell calcifications of lymph nodes and nodular calcifications of the spleen.

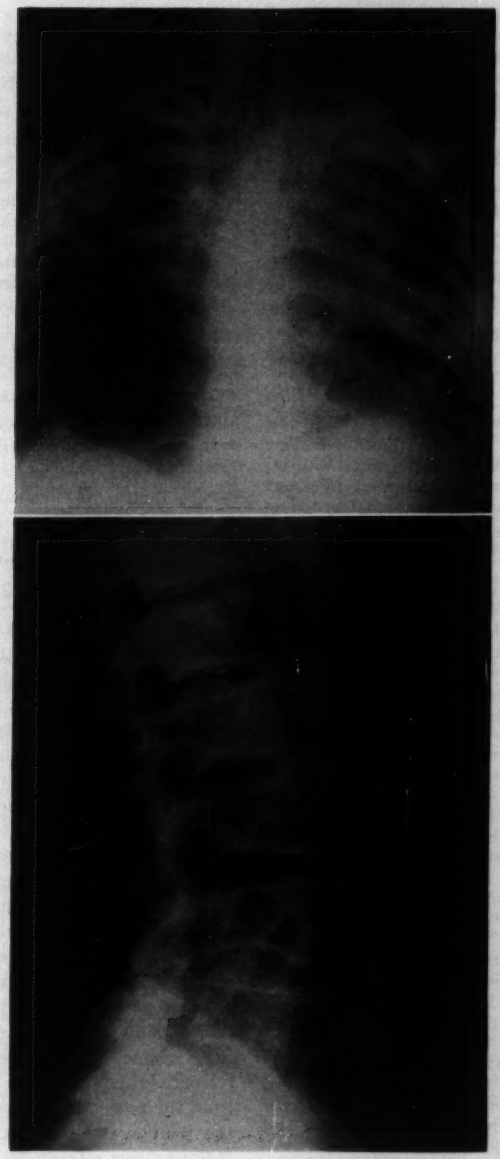


Case 1 (S.J.M.)

FIG. 3 (Upper). Photomicrograph of right supraclavicular lymph node showing whorls of hyalinized connective tissue with anthracotic pigmentation.

FIG. 4 (Center). Gross appearance of abdominal lymph node with egg-shell calcification and anthracotic pigmentation.

FIG. 5 (Lower). Photomicrograph of silicotic nodule in spleen showing concentric laminae of hyaline fibers with a layer of calcification.



Case 2 (N.P.W.)

FIG. 6 (Upper). Chest roentgenogram with arrows pointing to egg-shell calcifications of mediastinal and right supraclavicular lymph nodes.

FIG. 7 (Lower). Lateral roentgenogram of abdomen with arrows pointing to egg-shell calcification of peripancreatic lymph node.

(figure 5) and liver contained multiple areas of focal hyaline scarring and calcification. In the left frontoparietal region of the brain, a grayish-white mass about 5 cm. in diameter was found which, histologically, revealed metastatic squamous-cell carcinoma.

Comment: This patient with an occupational history of sand-blasting showed remarkable egg-shell calcifications of the supraclavicular, peribronchial, mediastinal, and abdominal lymph nodes due to silicosis, as well as calcification in the spleen and liver. He finally succumbed to metastatic squamous-cell carcinoma of the brain; the primary lesion was probably in the lungs but was not found because of the extensive scarring and calcification.

Case 2 (N.P.W.). The patient was a 72-year-old Negro male who noted a cough productive of clear mucoid sputum in 1943. Dyspnea appeared in 1944, and the chest roentgenogram showed bilateral midzonal infiltrations with enlarged hilar nodes. In 1945 he had swelling of the right elbow; the roentgenogram demonstrated destruction involving the radius and ulna, but smear and culture of the aspirate for acid-fast bacilli were negative. An arthrodesis was performed, and the soft tissue contained many epithelioid tubercles with central necrosis. In 1949 the patient received 35 gm. of streptomycin for recurrent drainage from the elbow, which resulted in healing. Occupational history revealed that the patient had worked in coal mines for two years in 1912 and 1913, and in a stone mill in 1925.

He was first admitted in 1950 because of productive cough and dyspnea. Many sputum specimens were negative for acid-fast bacilli on culture and guinea pig inoculation. The chest roentgenogram showed an increase of the density in the right upper lung and calcification of egg-shell variety in the right supraclavicular region and left lower lung medially. In 1954, carcinoma of the prostate was found.

The patient was readmitted to the hospital on March 8, 1959, because of increasing dyspnea. Temperature was 103° F., pulse 132 per minute, respirations 32 per minute, and blood pressure 160 systolic, 100 diastolic in mm. of mercury. Hard lymph nodes were palpable in the right supraclavicular region and left axilla. Dullness and crepitant rales were elicited in the upper halves of both lungs. The heart was enlarged and the right elbow was immobile. In the electrocardiogram, right bundle branch block was noted. The chest roentgenogram (figure 6) now showed possible cavitation in the right upper lung field in addition to the egg-shell calcifications. A lateral roentgenogram of the lumbar spine (figure 7) revealed similar calcification in the subdiaphragmatic region. A lymph node 1.5 cm. in diameter was removed from the right supraclavicular region which grossly was anthracotic and calcified and microscopically suggestive of an old healed granuloma. The patient had several febrile episodes, became azotemic, his general condition deteriorated, and he died on April 9, 1959.

Post-mortem examination showed massive pulmonary fibrosis, anthracosis, and heavy nodular calcification in both upper lung fields. Anthracotic pigmentation and calcification of egg-shell type were prominent in the enlarged peribronchial, mediastinal, and peripancreatic lymph nodes. The liver had an area of calcification, and the spleen contained miliary calcified nodules. Adenocarcinoma of the prostate with metastases to mesenteric nodes was present.

Comment: This patient probably had tuberculosis of the right elbow, although tubercle bacilli were never isolated. He had worked in coal mines and in a stone mill, and showed changes of silicosis with egg-shell calcifications in the supraclavicular, peribronchial, mediastinal, and peripancreatic lymph nodes, as well as calcifications in the spleen and liver. The cause of death was carcinoma of the prostate with metastases.

Discussion

Inhaled silica particles, 3 to 10 μ in diameter, may remain in the lung parenchyma, become immobilized in the lymph nodes, or disseminate to other organs, such as spleen, liver, and pericardium. Particles less than 3 μ in diameter may be eliminated in the urine (8). Doglioni (9) reported that 20 to 25 per cent of patients with silicosis had dissemination to the spleen, and suggested that silica entered the blood stream via the pulmonary lymphatics and thoracic duct.

However, Cunningham (10) describes lymphatics in the pig that drain from the diaphragmatic surfaces of the inferior lobes through vessels situated in the ligamentum pulmonale into the abdominal preaortic nodes. Contrary to Miller (11), Rouvière (12) and Tobin (13) have described similar lymphatic vessels in the pulmonary ligament in man. Edinger (14) implicates retrograde lymph flow in a patient with silicosis, from the posterior mediastinal lymph nodes into the peripancreatic nodes and the spleen. Cioni (15) confirms retrograde lymphatic transport to the abdominal nodes in a similar case. Such lymphatic drainage is probably due to blockage of the usual channels by connective tissue reaction to silica, as described by Gardner (8). The right supraclavicular nodes ordinarily drain the right lung and lower half of the left lung; and the left

supraclavicular nodes, the upper half of the left lung.

Thus, forward and retrograde lymphatic drainage can easily explain the finding of supraclavicular and abdominal silicotic lymph nodes, and the characteristic reaction to silica leads to egg-shell calcification of these nodes. Lymphatic spread may also account for the findings in the spleen and liver.

It should be noted that three of the five patients with abdominal egg-shell calcification eventually died of carcinoma, although different organs were involved. A possible relationship may exist but, in view of the small numbers, it must be regarded as fortuitous.

Summary

Two cases of extrathoracic egg-shell calcification of lymph nodes in silicosis, each involving the supraclavicular and abdominal nodes in addition to the pulmonary or mediastinal nodes, are reported. Only three patients with similarly calcified abdominal nodes and one with supraclavicular involvement have previously been recorded.

Retrograde lymphatic drainage due to blockage of the usual lymph channels, followed by the characteristic reaction to silica, appears to be the best explanation for the egg-shell calcification of the abdominal lymph nodes. Lymphatic spread also accounts for the findings in the supraclavicular nodes and possibly the changes in the spleen and liver.

Of the five patients with abdominal egg-shell calcification so far reported, three died of carcinomatosis, and a possible relationship may or may not exist.

Sumario

Calcificaciones Ovitestáceas Extratorácicas en la Silicosis

Se presentan 2 casos de calcificación extratorácica en cascarón de huevo de los ganglios linfáticos en la silicosis, afectando ambos los ganglios supraclaviculares y abdominales, además de los pulmonares o mediastínicos. No se habían descrito antes más que 3 enfermos con ganglios abdominales calcificados en forma semejante y uno con invasión supraclavicular.

El drenaje linfático retrógrado debido al bloqueo de los habituales conductos de la linfa, seguido de la típica reacción a la sílice, parece ofrecer la mejor explicación de la calcificación en cascarón de huevo de los ganglios linfáticos abdominales. La difusión linfática también explica los hallazgos en los ganglios abdominales, y posiblemente las alteraciones del bazo y del hígado.

De los 5 enfermos con calcificación abdominal en cascarón de huevo, que se han descrito hasta ahora, 3 fallecieron de carcinomatosis y puede haber o no una posible relación entre ambas cosas.

Resume

Calcifications extra-thoraciques en "coquille d'oeuf" dans la silicose

Les auteurs rapportent deux das de calcifications de ganglions lymphatiques extrathoraciques, en "coquille d'oeuf," au cours d'une silicose, chaque calcification intéressant des ganglions supraclaviculaires et abdominaux en plus de ganglions pulmonaires ou médiastinaux. On a signalé jusqu'à présent seulement trois malades avec des ganglions abdominaux calcifiés de cette façon et un comprenant un ganglion supraclaviculaire.

Un drainage lymphatique rétrograde dû au blocage des voies lymphatiques habituelles, suivi de la réaction caractéristique à la silice, semble être la meilleure explication de la calcification "en coquille d'oeuf" des ganglions lymphatiques abdominaux. L'envahissement lymphatique entre aussi en jeu dans la localisation dans les ganglions supraclaviculaires et peut-être les changements dans le foie et la rate.

Parmi les cinq malades ayant une calcification abdominale en "coquille d'oeuf", rapportés jusqu'à présent, trois moururent de carcinomatose, et ce peut être en relation ou non.

Acknowledgment

We should like to thank Dr. Harold Calvo-Nunez for his help in selecting and interpreting the histologic material.

REFERENCES

(1) Lommel, F.: Über Beurteilung und Verhütung der Silikose (Staublungenkrankheit), Deutsch Med Wschr., 1939, *65*, 871.

(2) Jacobs, L. G., Gerstl, B., Hollander, A. G., and Berk, M.: Intra-abdominal egg-shell calcifications due to silicosis, Radiology, 1956, *57*, 527.

(3) Grayson, C. E., and Blumenfeld, H.: "Egg-shell" calcifications in silicosis, Radiology, 1949, *53*, 216.

(4) Davies, T. W.: Silicosis in slate quarry miners, Tubercle, 1939, *20*, 543.

(5) Rigler, L. G.: The Chest. A Handbook of Roentgen Diagnosis, ed. 2, Year Book Publishers, Chicago, Illinois, 1954, p. 194.

(6) Sweany, H. C., Porsche, J. D., and Douglass, J. R.: Chemical and pathologic study of pneumoconiosis, with special emphasis on silicosis and silico-tuberculosis, Arch Path, 1936, *22*, 593.

(7) Riemer, A. D.: Egg-shell calcifications in silicosis, Amer J Roentgenol, 1945, *53*, 439.

(8) Gardner, L. U.: The pneumoconioses, Med Clin N Amer, 1942, *26*, 1239.

(9) Doglioni, L.: La silicosi della milza, Riv Anat Pat Oncol, 1957, *13*, 369.

(10) Cunningham, R. S.: On the development of the lymphatics of the lungs in the embryo pig, Carnegie Institute, Publication 224, 1916, p. 47.

(11) Miller, W. S.: The Lung, ed. 2, Charles C Thomas, Springfield, Illinois, 1947, p. 98.

(12) Rouvière, H.: Anatomy of the Human Lymphatic System, translated by M. J. Tobias, Edwards Brothers, Inc., Ann Arbor, Michigan, 1938, p. 94.

(13) Tobin, C. E.: Human pulmonic lymphatics: An anatomic study, Anat Rec, 1957, *127*, 611.

(14) Edinger, A.: Zur Kenntnis der Silikose der Milz, Zbl allg Path, 1932, *55*, 13.

(15) Cioni, C.: Sopra un caso di grave coniosi ad estesa diffusione: I. Lesioni polmonari, linfoghiandolari, splenische ed epatiche, Arch Ital Anat Istol Pat, 1943, *17*, 86.

ENLARGING PULMONARY HISTOPLASMOMA[1]

GERALD L. BAUM, ROBERT A. GREEN, AND JAN SCHWARZ

(Received for publication April 20, 1960)

Introduction

The finding of solitary pulmonary nodules ("coin lesions") in nonsymptomatic persons has been one of the more provocative results of chest roentgenography of large numbers of adults. Resection is often performed because of inability to make an absolute diagnosis by clinical, roentgenographic, or laboratory means. The accumulated pathologic material, especially from patients less than 45 years old, has resulted in a lower incidence of cancer (less than 50 per cent) and a higher incidence of granuloma than might be suspected (1–10).

The work of Puckett (11), using the periodic acid-Schiff stain, revealed histoplasmosis as one of the causes of granulomatous solitary pulmonary nodules. Confirmation of this work (12) and evaluation of large series of resected lesions revealed that histoplasmosis may well be the commonest cause of these granulomatous solitary nodules (2, 13) in many areas of the United States.

These lesions are usually morphologically inactive, and culture of the lesions is almost always sterile. Therefore, if the diagnosis could be made with certainty clinically or by roentgenography, pulmonary resection would be unnecessary. For this reason efforts at establishing diagnostic criteria have been made but, with the exception of the demonstration of laminated calcification within the lesions roentgenographically (posteroanterior, lateral, and/or laminagram), no reliable signs have resulted (13, 14). Previous chest films when available are often extremely helpful as it is generally agreed that the appearance of a new noncalcified lesion is suggestive of malignancy (15, 16), and the enlargement of a lesion seen previously indicates malignancy or active infection (2, 4, 5, 7).

[1] From the Pulmonary Disease sections of the Veterans Administration hospitals of Cincinnati, Ohio, and Ann Arbor, Michigan; the departments of Internal Medicine of the University of Cincinnati College of Medicine and the University of Michigan College of Medicine; and the Clinical Laboratories, Jewish Hospital, Cincinnati, Ohio.

The present writers have observed 4 cases of solitary histoplasmoma of the lung, all treated by resection, which had manifested roentgenographic growth over a period of years (table 1, figures 1–4). All of the present cases were inactive granulomas.

Case Reports

All patients were white males ranging in age from twenty-eight to forty-three years. Two cases were observed in Cincinnati; one in Ann Arbor, Michigan; and one in New York City. Three patients were entirely without symptoms while the fourth had symptoms of a vague nature, probably not related to the pulmonary nodule. Physical and laboratory examinations were normal in all patients.

Skin tests were done in the 4 patients; the histoplasmin test was positive in all and tuberculin in 3 of them. The complement-fixation test was negative in 2 patients. In the 2 others it was not done.

Two of the nodules were located in the left lower lobe, one in the right lower lobe, and one in the left upper lobe. Enlargement was seen over periods of 115, 54, 43, and 29 months.

Roentgenographically the lesions were well circumscribed at the beginning and at the end of observation. Calcification was demonstrated in only one patient preoperatively. One other patient had a suggestion of lamination of the lesion roentgenographically. It is of interest that all lesions showed both lamination and calcium deposits anatomically. In all patients the lesions were markedly dense.

In the 4 cases, resection was performed because the lesions seemed to enlarge. In all, wedge excision of the nodules was done. The postoperative course of each patient was benign, and all are now well and working with follow-up observation of 34, 31, 20, and 6 months.

Pathology: All lesions had essentially similar characteristics. There was a fibrous capsule surrounding and completely circumscribing them. There was pleural thickening to a striking degree where the lesions contacted the surface. The central portion contained amorphous material with calcium deposits, and organisms morphologically identical with *H. capsulatum* were demonstrated in all 4 patients with the Grocott silver stain (17). (This has proved to be the most useful of the special stains in identifying yeast cells in tissue.) Within the capsules, minimal lymphocytic infiltrate was seen, but no tubercles

TABLE 1

FOUR CASES OF ENLARGING HISTOPLASMOMA

Case Number, Race, Sex	Clinical Findings	Skin Test	Complement-Fixation Test	Roentgenogram		Time	Pathologic Findings	Follow-up Observations
				Initial Size	Final Size			
1. White male, 41 years	6 months, epigastric pain; chest colds; 10-lb. weight loss	Histoplasmin +* PPD + Blastomycin +	Not done	2.0 cm. (RLL)†	3.5 cm.	115 months	Healed with *H. capsulatum* in center; negative culture of caseous core; calcific deposits	31 months, well and working
2. White male, 37 years	No symptoms or physical signs	Histoplasmin + PPD +	Not done	1.5 cm. (LUL)†	2.0 cm.	29 months	Healed with *H. capsulatum* in center of caseous core; calcific deposits	34 months, well and working
3. White male, 28 years	No symptoms or physical signs	Histoplasmin + OT −* Blastomycin − Coccidioidin −	Negative	1.5 cm. (LLL)†	2.5 cm.	43 months	Healed; laminated; some irregular calcification; *H. capsulatum* seen	6 months, well
4. White male, 43 years	No symptoms or physical signs	Histoplasmin + PPD +	Negative	1.5 cm. (LLL)	2.5 cm.	54 months	Healed; laminated; *H. capsulatum* seen. Culture negative	20 months, well

* + = positive
− = negative
† RLL = right lower lobe
LUL = left upper lobe
LLL = left lower lobe

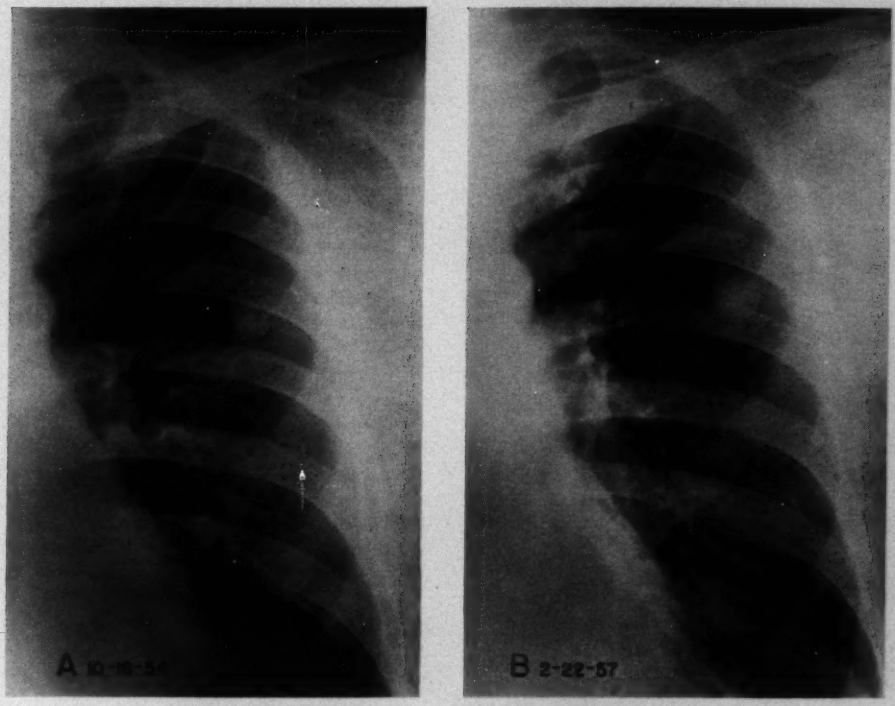


FIG. 1. *Case 2*, showing growth of lesion in left upper lobe.

FIG. 2. *Case 4* showing histoplasmoma *in situ* at thoracotomy. Note adhesions between lobes, circumscribed nature of the lesion, and the thickened overlying pleura.

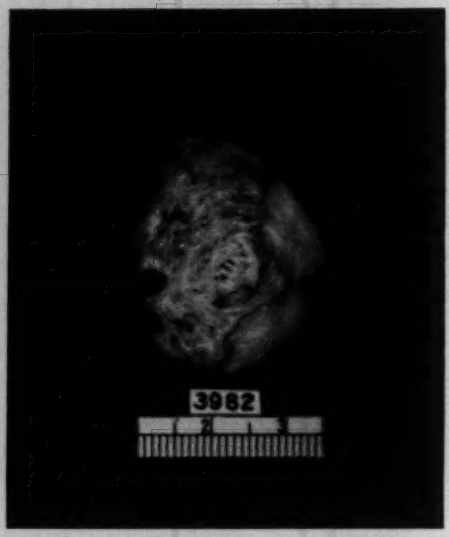


FIG. 3. *Case 1*, showing gross cross section of resected specimen. Overlying pleural plaque and lamination of peripheral fibrous tissue are striking.

were noted. Outside the lesion, no evidence of activity manifested by infiltrate and/or tubercle formation was present. Within the focus surrounded by the fibrous tissue, concentric calcification was evident. There was no perifocal activity in the surrounding pulmonary tissue.

DISCUSSION

In 4 patients manifesting enlarging solitary pulmonary nodules, typically inactive histoplasmomas have been discovered on resection. The roentgenographic enlargement of lesions seen to be histologically inactive appears paradoxic, at first glance. Since there was complete absence of perifocal edema, inflammation, or tubercles outside or within the capsules, enlargement due to recent active inflammation was excluded. The incorporation of satellite lesions as an explanation for enlargement was not possible due to the unbroken rounded circumscribed appearance of the lesions. Therefore it was concluded that inflammatory activity could not possibly explain the roentgenographic characteristics of these lesions.

Culturally, the impression of inactivity is strengthened since both the central amorphous material and the capsule were sterile; this in spite of the demonstration of the organism on microscopy with special stains.

It is believed that increasing fibrosis with hyaline change and/or mineral salt deposition in the periphery of the focus would increase the density of this portion of the lesion and appear roentgenographically as increase in size.

Although clinical findings are frequently of little significance in evaluation of activity of a pulmonary lesion, it is of interest that 3 of the 4 patients were entirely without symptoms, and the complaints of the fourth were mild and had no specific reference to the lungs.

Histoplasmin skin tests were positive. This finding has much less importance in the endemic area than it does in areas in which positive skin tests are unusual. Complement-fixation tests were negative in the 2 cases in which the test was done. It is the writers' impression that this is usually the case in histoplasmomas.

Therefore, it is believed that the characteristic pulmonary histoplasmoma is an inactive lesion. Although not definitely explained, the circumstance of apparent growth shown roentgenographically does not alter this conclusion.

In the cases presented here, apparent enlargement was observed roentgenographically, but the inference that this enlargement implied activity of the lesion or presence of malignancy was wrong. This observation of growth in nonactive inflammatory lesions (2, 7) and benign tumor (18) has been noted before. This experience adds further to the difficulty of making preoperative diagnoses of solitary pulmonary nodules. It is not intended to discourage indicated exploration of undiagnosed nodules. However, since as many as 70 per cent of lesions resected in some series in younger patients have been benign, the physician should be aware of the possibility of enlarging histoplasmoma and need not think it imperative to perform immediate thoracotomy in young patients with positive skin tests and dense lesions in whom the diagnosis of histoplasmoma seems reasonable.

SUMMARY

Four cases of "enlarging" histoplasmomas are presented. The inactive nature of all of these lesions morphologically is pointed out. The suggested explanation for the roentgenographic finding in these cases is gradual change in the

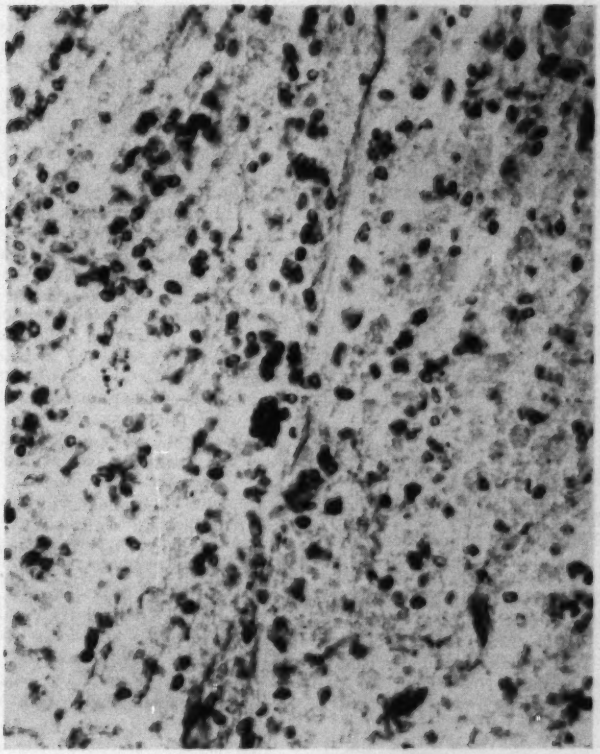


FIG. 4. *Case 2.* Grocott stain of amorphous core reveals myriads of yeast cells of *H. capsulatum.*

density of the periphery of the granulomatous tissue.

Slowly enlarging pulmonary lesions of marked density in younger persons are not necessarily malignant or active infections, and do not constitute invariable indications for surgery.

SUMARIO

Histoplastoma Pulmonar Creciente

Preséntanse 4 casos de histoplastoma pulmonar en vías de agrandamiento. Señálase la naturaleza inactiva de todas estas lesiones morfológicamente. La explicación propuesta para el hallazgo radiográfico en estos casos es la alteración gradual del espesor de la periferia del tejido granulomatoso. Las lesiones pulmonares de acentuada densidad que aumentan paulatinamente de tamaño en las personas jóvenes no son forzosamente infacciones malignas o activas, y no constituyen indicaciones invariables para la cirugía.

RESUME

Histoplasmose pulmonaire s'élargissant

Les auteurs présentent quatre cas d'histoplasmose "s'élargissant." La nature inactive de toutes ces lésions est signalée morphologiquement. L'hypothèse expliquant les données radiographiques dans ces cas est un changement graduel dans la densité de la périphérie du tissu granulomateux. Des lésions pulmonaires très denses, s'élargissant lentement, chez de jeunes personnes, ne sont pas nécessairement des infections malignes ou actives, et ne constituent pas invariablement des indications chirurgicales.

Acknowledgment

The writers wish to thank Dr. Henry Felson for allowing them to study and report the two Cincinnati cases.

REFERENCES

(1) BRISTOW, J. D., AND GAULDEN, E. C.: Three cases of circumscribed pulmonary opacities simulating tumor, Dis Chest, 1956, *30*, 96.

(2) Davis, E. W., Peabody, J. W., and Katz, S.: The solitary pulmonary nodule: A ten-year study based on 215 cases, J Thor Cardiov Surg, 1956, *32*, 728.

(3) Effler, D. B., Blades, B., and Marks, E.: The problem of the solitary lung tumors, Surgery, 1948, *24*, 917.

(4) Good, C. A., and Wilson, T. W.: The solitary circumscribed pulmonary nodule: Study of seven hundred five cases encountered roentgenologically in a period of three and one half years, JAMA, 1958, *166*, 210.

(5) Greer, A. E., Carey, J. M., and Zuhdi, N.: Expeditious evaluation of circumscribed pulmonary shadows, JAMA, 1959, *171*, 1783.

(6) Holin, S. M., Dwork, R. E., Glaser, S., Rikli, A. E., and Stocklen, J. B.: Solitary pulmonary nodules found in a community-wide chest roentgenographic survey, Amer Rev Tuberc, 1959, *79*, 427.

(7) Hood, R. T., Good, C. A., Clagett, O. T., and McDonald, J. R.: Solitary circumscribed lesions of the lung: Study of 156 cases in which resection was performed, JAMA, 1953, *152*, 1185.

(8) Paulson, D. L.: The importance of the pulmonary nodule, Minnesota Med, 1956, *39*, 127.

(9) Sharp, D. V., and Kinsella, T. J.: The significance of the isolated pulmonary nodule, Minnesota Med, 1950, *33*, 886.

(10) Wilkins, E. W.: The asymptomatic isolated pulmonary nodule, New Engl J Med, 1955, *252*, 515.

(11) Puckett, T. F.: Pulmonary histoplasmosis: A study of 21 cases with identification of *H. capsulatum* in resected lesions, Amer Rev Tuberc, 1953, *67*, 453.

(12) Zimmerman, L. E.: The demonstration of Histoplasma and coccidioides in so-called tuberculomas of the lung: A preliminary report on 35 cases, AMA Arch Int Med, 1954, *94*, 690.

(13) Peabody, J. W., Katz, S., and Davis, E. W.: Patterns of calcification within the solitary pulmonary nodule a valuable guide to therapy, Tran 17th Conf on Chemother Tuberc, VA–Armed Forces, 1958, p. 173.

(14) O'Keefe, M. E., Good, C. A., and McDonald, J. R.: Calcification in solitary nodules of the lung, Amer J Roentgenol, 1957, *77*, 1023.

(15) Rigler, L. G.: A roentgen study of the evolution of carcinoma of the lung, J Thor Cardiov Surg, 1957, *34*, 283.

(16) Vance, J. W., Good, C. A., Hodgson, C. H., Kirklin, J. W., and Gage, R. P.: The solitary circumscribed pulmonary lesion due to bronchogenic carcinoma: A 3-year follow-up study of 94 surgically treated patients, Dis Chest, 1959, *36*, 231.

(17) Grocott, R. G.: A stain for fungi in tissue sections and smears: Using Gomori's methenamine-silver nitrate technique, Amer J Clin Path, 1955, *25*, 975.

(18) Weisel, W., Glicklich, M., and Landis, F. B.: Pulmonary hamartoma, enlarging neoplasm, AMA Arch Surg, 1955, *71*, 128.

CHEST CONFERENCE

University of California School of Medicine

CASE UCH 295764

DR. ARTHUR HALLIDAY[1]: A 23-year-old woman was admitted to the hospital on September 16, 1959, because of increasing fatigue and shortness of breath of two months' duration.

History: The patient's symptoms, consisting of fatigue, dyspnea, a dull retrosternal aching pain, and palpitations on exertion, had gradually increased in severity. Six weeks previously she had developed a severe nonproductive hacking cough which was aggravated by deep inspiration.

The patient had lived in Oklahoma until the age of ten years and then moved to California. Her father had died ten years ago of proved pulmonary cryptococcosis.

Physical examination: The patient was a well-developed, well-nourished young woman who was tachypneic at rest. The temperature was 37°C., pulse rate, 114 per minute; respirations, 24 per minute; and blood pressure, 110/72 mm. Hg. She became dyspneic on walking across the room, but did not develop cyanosis during exercise. The lateral chest expansion was only one inch, the thorax was resonant to percussion, and crepitant rales were heard at both bases. On examination of the heart, the patient had sinus tachycardia and splitting of the basal second sound with accentuation of the pulmonic component.

Laboratory findings: The leukocyte count was 11,400, and the packed cell volume 50 per cent. The urine was normal. Serum albumin was 3.9 gm. and globulin 4.5 gm. per 100 ml.; on paper electrophoresis, the gamma globulins were 22 per cent of the total serum proteins (normal, 16 ± 4 per cent). Total serum calcium was 6.1, 5.65, and 5.45 mEq. per L. on three occasions (normal range, 4.8 to 5.65 mEq. per L.), and serum phosphorus 4.9 mg. per 100 ml. No lupus erythematosus cells were found on two examinations of peripheral blood. Intermediate-strength PPD tuberculin, histoplasmin, coccidioidin, and blastomycin skin tests were negative. Three gastric washings were negative for acid-fast bacilli after three months of culture. Bilateral diffuse and patchy parenchymal infiltrations were seen in an X-ray film of the chest taken on September 21 (figure 1*A*). The same day a right scalene fat pad dissection was performed. On histologic examination of the four lymph nodes (figure 2) in the specimen, multiple noncaseating granulomas were found. Stains of the tissue for acid-fast organisms and fungi were negative. The results of pulmonary function studies on September 23 and on two subsequent occasions are given in table 1. A regimen of 40 mg. of prednisone[2] daily was instituted, and the patient was discharged on September 24.

Course: When next seen on October 16 in the clinic, the patient stated that the fatigue, dyspnea, and cough had disappeared one week after she had left the hospital and that she had noted acne, rounding of the face, painless swelling of the knees, and a 13-pound gain in weight. On examination, the pulse was 116 per minute; respirations, 18 per minute; and blood pressure 120/80 mm. Hg. The patient was euphoric, and acne and rounding of the face were evident. The lateral chest expansion was now 2 inches; on percussion and auscultation the lungs were clear. A small effusion of the left knee joint was noted. An X-ray film of the chest (figure 1*B*) showed remarkable clearing of the infiltrates. Pulmonary function studies were repeated at this time (table 1). The dose of prednisone was reduced to 30 mg. daily; she was given 3 gm. of potassium chloride daily and a diet containing 1 gm. of sodium was prescribed.

On December 3, the patient was readmitted to the hospital for six days for follow-up studies. At this time she stated that she had no symptoms and felt well. The only abnormality on physical examination was splitting of the basal second sound with accentuation of the pulmonic component. An X-ray film of the chest was interpreted as normal. Serum calcium was 5.3 mEq. per L., and phosphorus 3.7 mg. per 100 ml. Serum albumin was 5.3 and globulin 2.4 gm. per 100 ml. Pulmonary function studies were again done on the following day (table 1). A left scalene fat pad biopsy was performed on December 5; microscopic sections showed only reticuloendothelial hyperplasia.

The dose of prednisone was gradually reduced and was discontinued entirely on April 14, 1960. There has been no roentgenographic evidence of recurrence, and the patient has remained well.

DISCUSSION

DR. CHARLES T. CARMAN[3]: This case is particularly instructive because it provides an unusual opportunity to correlate the patient's symptoms and physical signs with specific abnormalities of pulmonary function.

The findings on clinical examination of tachypnea, restricted lateral chest expansion, fine basilar rales, tachycardia, and accentuation of the pulmonic component of the basal second sound in a young woman with a history of fatigue, dyspnea, and severe nonproductive cough indicate the presence of restrictive lung disease and pulmonary hypertension. The additional roentgeno-

[1] Assistant resident in Medicine.

[2] Supplied as Meticorten by Schering Corporation, Bloomfield, New Jersey.

[3] Assistant Professor of Medicine.

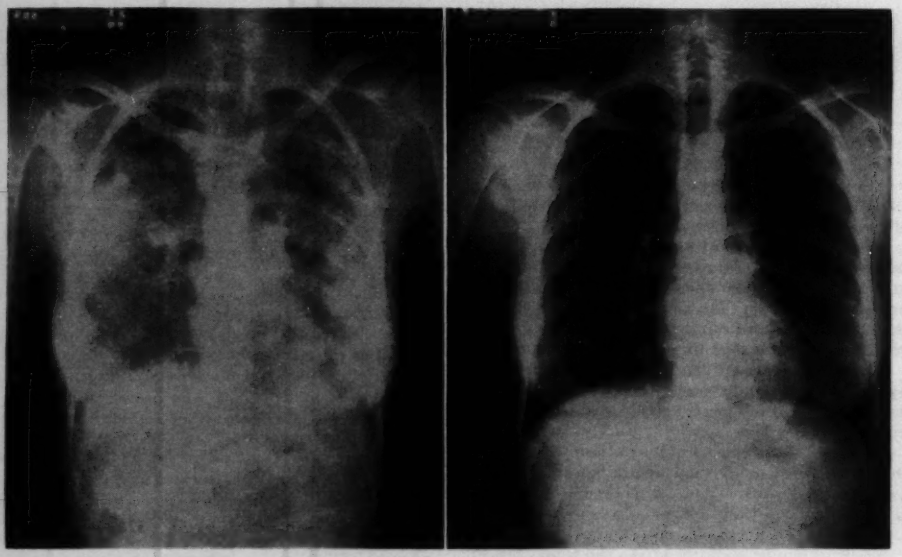


FIG. 1 (*A*) (Left). Roentgenogram of the chest on September 21, 1959, before treatment. (*B*) (Right). Roentgenogram of the chest on October 16, 1959, after 16 days of steroid therapy.

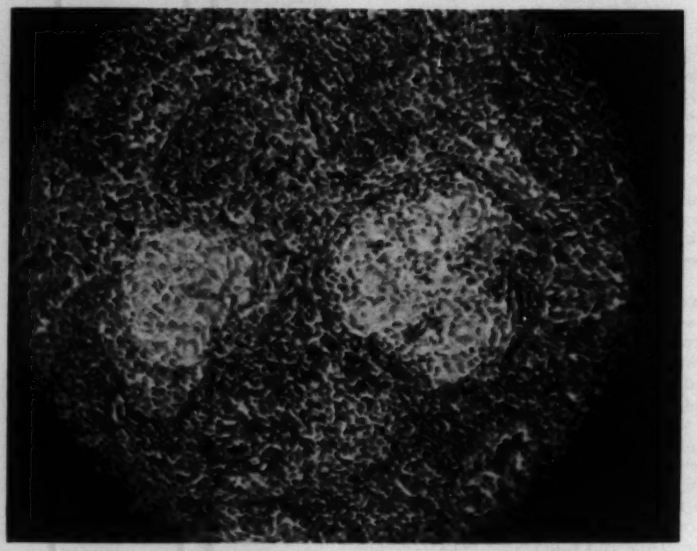


FIG. 2. Microscopic section of scalene lymph node showing noncaseating granulomas (× 200).

graphic evidence of widespread pulmonary infiltration suggests a more specific entity—the syndrome of alveolar-capillary block. This clinical impression is confirmed by the first pulmonary function study (table 1), which shows markedly decreased lung volumes and diffusing capacity, minor abnormalities in the distribution of gas, slight reduction of partial pressure of carbon

dioxide (Pa_{CO_2}) and arterial oxygen saturation (Sa_{O_2}), and normal flow rates. This combination of clinical and physiologic features is characteristic of the alveolar-capillary block syndrome (1).

Unfortunately, this conclusion is of limited value in making an etiologic diagnosis, since the alveolar-capillary block syndrome occurs in a wide variety of diseases (2). However, the borderline elevation of serum calcium and gamma globulin levels, the negative tuberculin skin test, and the biopsy report of multiple noncaseating granulomas permit us to make the additional diagnosis of sarcoidosis.

After three weeks of steroid therapy, the patient's pulmonary symptoms had disappeared and no abnormalities were found by physical and X-ray examination of the lungs. A pulmonary function study at this time showed that, although the lung volumes were now normal, the diffusing capacity had not changed.

The favorable clinical and physiologic responses to treatment lead us to question the reason for the patient's dyspnea. It probably was not caused by bronchial obstruction since the flow rates were relatively normal; or by chemical stimuli since the Pa_{CO_2} was not elevated and the Sa_{O_2} was only slightly reduced; or by the low diffusing capacity, which remained unchanged when the patient was no longer dyspneic. The dyspnea was present, however, when the lung volumes were reduced, and disappeared when they returned to normal. In a study of 23 patients with diffuse pulmonary sarcoidosis, Lyons (3) found significant reductions in vital capacity, total lung capacity, and pulmonary compliance (decreased distensibility of the lungs). He demonstrated that these changes are sometimes reversed by steroid therapy, as in this case. The cause of the dyspnea in this patient, therefore, probably was an exaggeration of the normal Hering-Breuer reflex due to decreased distensibility of the lungs. A similar mechanism may account for the dyspnea of pulmonary edema and pulmonary fibrosis, in which the elastic properties of the lung are altered by the presence of fluid or fibrosis in the interstitial tissue. The fact that changes in vital capacity reflect changes in pulmonary compliance, as shown by Lyons (3), provides a simple method of documenting the response to therapy.

DR. ROBERT O'REILLY: Why does the diffusing capacity fail to change after steroid therapy?

The diffusing capacity of the lungs is dependent on two factors: the total surface area and the permeability per unit area of the alveolar-capillary membrane (4). In sarcoidosis, diffuse infiltration of the interstitial pulmonary tissue might interfere with diffusion in two ways: (*a*) by obliterating pulmonary capillaries, which would reduce the total surface area available for diffusion, and (*b*) by producing a thickening of the alveolar-capillary membrane, which would decrease its permeability per unit area. Capillary obliteration, which would be largely irreversible, is probably chiefly responsible for the impaired diffusing capacity in sarcoidosis. Thickening of the alveolar-capillary membrane, which is at

TABLE 1

PULMONARY FUNCTION STUDIES*

	Predicted	9/23/59	10/16/59	12/4/59
Lung volumes				
Vital capacity (ml.)	3,325	1,650	3,490	3,800
Total lung capacity (ml.)	4,150	2,250	5,050	4,780
RV/TLC†	20%	13%	18%	20%
Functional residual capacity (ml.)	1,656	1,440	2,970	2,700
Distribution of gas and blood				
N_2 increase (750–1,250 ml.)	2.0%	5.5%	2.3%	2.7%
N_2 after 7 min. of O_2	2.5%	1.0%	0.7%	1.0%
Diffusion				
D_{CO} (ml./min./mm. Hg.)	22.4	11.5	11.6	10.7
Arterial blood				
Sa_{O_2}	96–99%	93%	96%	96%
Pa_{CO_2} (mm. Hg.)	38–42	34	—	35
Mechanics of breathing				
Maximal flow rate (L./min.)				
Expiratory	400	330	330	375
Inspiratory	300	250	300	333

* Performed by Dr. Karlman Wasserman and Dr. Jerome G. Green of the Cardiovascular Research Intsitute

† Residual volume/total lung capacity

least partially reversible, is probably more closely related to the changes in pulmonary compliance. Such an explanation is consistent with the lack of change in the diffusing capacity after the administration of steroids.

Siltzbach (5) recently summarized the indications for steroid therapy in sarcoidosis. In the present case, the definite indications for use of steroids consisted of the recent onset of the disease, the miliary dissemination in the lungs, and the presence of the alveolar-capillary block syndrome.

The degree of response to steroids in sarcoidosis appears to be directly proportional to the duration of the disease (6–8) and to the evolutionary stage of the pathologic changes in the pulmonary parenchyma. Acute cases, in which the pathologic process is an active progressing granuloma, often respond favorably; chronic cases, in which spontaneous healing with extensive hyalinization and fibrosis have already occurred, frequently do not.

The effect of steroids on the eventual fate of pulmonary lesions in sarcoidosis has not been convincingly demonstrated. Several writers (6, 9, 10) have reported that hyalinization and fibrosis may be augmented by treatment. Unless lung biopsies are performed before and after therapy, however, the effects of treatment cannot be differentiated with certainty from the natural variations in the histologic pattern of the disease.

The symptomatic response to treatment, when it takes place, is usually prompt. As in this case, improvement can then be documented by the occurrence of gross roentgenographic and physiologic changes within four to six weeks.

Dr. Charles T. Carman's diagnosis:

Sarcoidosis of lung and lymph nodes
Alveolar-capillary block syndrome

DR. ELLEN BROWN: Is this a typical response to steroid therapy in acute pulmonary sarcoidosis?

DR. CHARLES T. CARMAN: Unfortunately, no! This is by far the most rapid and complete response to treatment I have encountered. Luckily for this patient, her disease began abruptly with diffuse pulmonary involvement which soon produced acute respiratory symptoms and forced her to seek medical care. She was therefore treated very early in the course of the disease, and I think this accounts for the dramatic response. Since the onset of sarcoidosis is usually insidious and the symptoms mild, most patients are not seen until the disease is much more advanced.

SENIOR STUDENT: Do you think the X-ray features in this case are typical of sarcoidosis?

DR. CHARLES T. CARMAN: I would say yes, with the qualification that there is no typical roentgenographic picture in sarcoidosis. In a review of the roentgenographic appearance of the lungs in 109 cases of early pulmonary sarcoidosis, Siltzbach (11) found diffuse bronchopneumonic infiltrations, similar to those seen in this case, in 14 patients, diffuse miliary nodules in 33, and bilateral hilar lymph node enlargement in 62. It should be emphasized that frequently there is little correlation between a patient's symptoms and the roentgenographic appearance of the lungs. A common observation in sarcoidosis is that the "X-ray is sick, but the patient is well."

CHARLES T. CARMAN, Editor
MARY MORROW, Assistant Editor
University of California School of Medicine
San Francisco, California

August 1, 1960

REFERENCES

(1) AUSTRIAN, R., MCCLEMENT, J. H., RENZETTI, A. D., JR., DONALD, K. W., RILEY, R. L., AND COURNAND, A.: Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion: The syndrome of "alveolar-capillary block," Amer J Med, 1951, *11*, 667.

(2) BADER, M. E., AND BADER, R. A.: Editorial: The alveolar-capillary block syndrome, Amer J Med, 1958, *24*, 493.

(3) LYONS, H. A.: Pulmonary compliance in granulomatous disease of the lung, Amer J Med, 1958, *25*, 23.

(4) RILEY, R. L., RILEY, M. C., AND HILL, H. MCD.: Diffuse pulmonary sarcoidosis: Diffusing capacity during exercise and other lung function studies in relation to ACTH therapy, Bull Johns Hopkins Hosp, 1952, *91*, 345.

(5) SILTZBACH, L. E.: Editorial: Progress in sarcoidosis, Amer J Med, 1957, *22*, 841.

(6) SILTZBACH, L. E.: Effects of cortisone in sarcoidosis: A study of thirteen patients, Amer J Med, 1952, *12*, 139.

(7) SOUDERS, C. R., AND AFFOLTER, H. P.: Steroid therapy in pulmonary sarcoidosis, Lahey Clin Bull, 1957, *10*, 178.

(8) RUDBERG-ROOS, I., AND ROOS, B. E.: Pulmonary function in sarcoidosis before and after ACTH and cortisone therapy, Acta Tuberc Scand, 1958, *35*, 49.

(9) STONE, D. J., SCHWARTZ, A., FELTMAN, J. A., AND LOVELOCK, F. J.: Pulmonary function in sarcoidosis: Results with cortisone therapy, Amer J Med, 1953, *15*, 468.

(10) MCCLEMENT, J. H., RENZETTI, A. D., HIMMELSTEIN, A., AND COURNAND, A.: Cardiopulmonary function in the pulmonary form of Boeck's sarcoid and its modification by cortisone therapy, Amer Rev Tuberc, 1953, *67*, 154.

(11) SILTZBACH, L. E.: Pulmonary sarcoidosis, Amer J Surg, 1955, *89*, 556.

Notes

TUBERCULIN SENSITIVITY OF PHYSICIANS

While tuberculin testing is common in schools of medicine, there is almost no information on the frequency of tuberculous infection among physicians following internship, residency, and periods of clinical practice. This is because there are no opportunities for systematic mass testing of physicians. The occupational risk of exposure has been assumed to be considerable in all fields of practice which involve contact with physically ill people, although in such fields as orthopedic surgery and dermatology, as contrasted with general practice, pathology, and phthisiology, the risk is probably small. Reid[1] has shown that tuberculosis morbidity in the United Kingdom is excessive among pathologists and laboratory technicians. On the other hand, mortality from tuberculosis in the United States is far lower in the medical profession than in the general population.[2] The limited data available suggest that the same may be true of nurses.[3] This paradox might be explained in part by socio-economic factors; in part, by the better opportunity for early diagnosis and adequate therapy which these groups may enjoy. Thus, the mortality rates completely fail to reflect the risks of infection and morbidity.

A practical question today is whether BCG vaccination ought to be recommended for students of medicine and nursing. Data on the actual risk of infection in the course of the practice of medicine and nursing would be helpful in answering this question.

It is for these reasons that even fragmentary information on a heterogeneous group may be worthy of presentation.

Over the past nine years, students at the Johns Hopkins School of Hygiene and Public Health have been systematically tested with tuberculin. This was done during their course of instruction in epidemiology as a practical exercise to illustrate the variability in the interpretation of tuberculin reactions. A few students, averaging one or two per class, declined the test because they had experienced severe reactions in the past, and a few others failed to be tested because of absence on the scheduled day.

Two-thirds of the students are physicians, all of whom have had some postgraduate hospital training and some of whom have been in clinical practice for a number of years, while others entered public health almost immediately after their internships. Very few have received BCG vaccine. The remaining third are from other professional fields: nurses, dentists, sanitary engineers, veterinarians, statisticians, and graduate students in the biologic sciences. Only nurses are separately identified in this report, not because they outnumber the other groups but because of their presumed occupational hazards. Most of them have done some bedside nursing since graduation, but a greater part of their careers has been in public health work, which may entail some exposure in the homes of patients.

The data to be presented are too meager in numbers to justify analysis according to any more precise measure of exposure than categorizing the subjects into these two professional groups and all others. The influence of age and of residence must, however, be taken into account. Of 426 persons tested, 254 (60 per cent) were from the United States. The remainder came from many other countries, chiefly the Americas, Europe, and certain Asian countries (particularly India, the Philippines, and Japan). The distribution of persons tested as to national origin, professional group, age, and sex did not vary materially from year to year.

All tests were done by the Mantoux technique employing 0.00002 mg. (1 TU) of PPD from a single commercial source. Reactions measuring 5 mm. or more in transverse diameter of induration were considered positive. Multiple readings were made each year and in some years, multiple tests; but only the first reading of a single test was used in the analysis. Readings by a single individual (P.S.) were employed in seven of the nine years.

No time trend in the prevalence of tuberculin sensitivity over the nine-year period is evident. The year-to-year fluctuations are within the limits of chance.

The data for the nine-year period classified according to professional groups, nationality, and age are presented in table 1. Because the dose of tuberculin was small and because the experience of previous severe reactions dissuaded a few persons from taking the test, the figures probably slightly underestimate the true frequency of infection.

[1] Reid, D. D.: Brit Med J, 1957, *2*, 10.

[2] Dickinson, F. G., and Martin, L. W.: JAMA, 1956, *162*, 1462.

[3] Theodore, A., *et al.*: J Chron Dis, 1956, *4*, 111.

TABLE 1

TUBERCULIN SENSITIVITY OF STUDENTS BY PROFESSIONAL GROUP, NATIONALITY, AND AGE

Age Group	United States			Other Countries		
	Number Tested	Number of Reactors	Per Cent of Reactors	Number Tested	Number of Reactors	Per Cent of Reactors
Physicians						
25–29	28	9	32	25	19	76
30–39	77	30	39	82	69	84
40 and older	32	25	78	35	27	77
Total	137	64	47 (46)	142	115	81 (80)
Nurses—all ages	29	7	24 (23)	4	3	
Other professions—all ages	88	26	30 (31)	26	16	62 (66)

Figures in parentheses are percentages of reactors age-adjusted by the indirect method to the age distribution of the whole tested group.

Two striking points are revealed by this table: one is the great difference in reaction-frequency between United States residents and persons in the same professional categories from other countries (for physicians, 46 and 80 per cent, respectively; for other professions, 31 and 66 per cent, respectively). It is unfortunate that the small number of students from any one area precludes more specific comparison by area of residence, but the differences clearly indicate the excessive exposures which the foreign students as a group have sustained. The second point is the contrast between the reaction-frequency of physicians and that of other professional groups, supporting the view that physicians do have an occupational liability to infection.

The sharp rise in percentage of reactors more than forty years old among American physicians is thought to reflect not only an age effect but also the greater opportunity for infection that existed in earlier years. Thus, physicians tested at age fifty were exposed, prior to entering medical school, to the risks which prevailed from about 1910 to 1930 and to occupational risks from about 1930 onward. There is much evidence that the prevalence of open—and especially undetected—tuberculosis as encountered in hospitals, clinics, and practice is declining.

It would be unwise to venture any strong opinion on whether medical students should receive BCG vaccination on the basis of this highly selected and limited material. The advantages of being able to detect infection early through regular tuberculin testing versus the protection conferred by vaccination have been widely debated. The writer's opinion is that vaccination of medical students in the United States is still advantageous, but that in a relatively short period of time the risk may be so low as to warrant discontinuation of vaccination, especially if periodic tuberculin testing is substituted. The hazard for practitioners in some other countries appears still to be large.

PHILIP E. SARTWELL[4]
Department of Epidemiology
The Johns Hopkins University School of Hygiene and Public Health
Baltimore 5, Maryland

August 1, 1960

[4] The assistance of Hermine G. Bird in this study is gratefully acknowledged.

A COMPARATIVE STUDY OF THE ANILINE–CYANOGEN BROMIDE AND O-TOLIDINE–CYANOGEN BROMIDE DIRECT QUALITATIVE MICRO-NIACIN TESTS FOR DIFFERENTIATING HUMAN TUBERCLE BACILLI FROM OTHER MYCOBACTERIA

Results Obtained Using Fresh Cultures

In a previous investigation[1] it was demonstrated that a micro-niacin test was useful for differentiating human tubercle bacilli from other mycobacteria. Gutiérrez-Vázquez[2, 3] reported a similar procedure in which *o*-tolidine and cyanogen bromide were used as the test reagents instead of aniline and cyanogen bromide. The present study was undertaken to compare both of these tests.

Twenty strains of freshly isolated human tubercle bacilli, 2 strains of bovine tubercle bacilli, 2 strains of avian tubercle bacilli, 20 strains of unclassified acid-fast bacilli, and 5 strains of saprophytic mycobacteria were selected for study. These organisms were supplied through the courtesy of other workers.[1]

The human tubercle bacilli and the unclassified mycobacteria were isolated from various clinical specimens such as sputum specimens, bronchial washings, gastric lavages, resected lung lesions, pleural fluids, lymph nodes, and catheterized ureteral urines. Of the 20 unclassified strains, 10 were photochromogens, 5 were scotochromogens, and 5 were Battey types. All the organisms were transferred to Löwenstein-Jensen[4] and Proskauer-Beck[4] media to maintain stock cultures.

Medium and inocula: The Tween®-albumin niacin test medium and inocula described previously[1] were used to perform all of the niacin tests. Eight sets of the medium were inoculated with 0.3-ml. aliquots of each strain and then placed into the 37°C. incubator in a nearly horizontal position to permit uniform distribution of the inocula. Niacin tests were performed on the cultures after seven, ten, fourteen, and twenty-one days, respectively.

Preparation of water extracts: From 2 to 10 drops of distilled water were added to each culture, depending on the amount of fluid already present. The tubes were then placed in a nearly horizontal position for approximately five minutes to enable the fluid to cover the entire surface of the bacterial mass, thus permitting greater extraction of niacin. After this time, the extract from each culture was removed by means of separate 8-inch disposable plastic straws fitted with a removable rubber aspirating bulb[1] and placed into 10- × 100-mm. serologic tubes. All of the tubes containing the extracts were then sterilized for fifteen minutes at fifteen pounds' pressure and cooled to room temperature.

The micro-plate method: Two drops of extract from each strain were removed from the serologic tubes by means of separate plastic straws and placed into appropriately marked depressions in white glazed porcelain spot plates. To each extract in the depression to the left was added 1 drop of 4 per cent volume/volume aniline in 95 per cent ethanol and to each extract in the depression to the right was added 1 drop of 1.5 per cent weight/volume *o*-tolidine in 95 per cent ethanol. Then to all the depressions was added 1 drop of a 10 per cent weight/volume aqueous solution of cyanogen bromide. The contents were mixed by sliding the plates back and forth in a rotary motion, care being taken to prevent spillage.

The results were read in approximately five minutes after mixing the reagents with the extracts, using a reflected fluorescent light source. The results were graded arbitrarily as follows:

Aniline-cyanogen bromide (A-CB) method:

− = negative, no color.
D = doubtful, questionable distinct yellow color.
+S, +M, +I = positive, distinct yellow color; reaction either slight, moderate, or intense, depending on the degree of coloration.

O-tolidine-cyanogen bromide (OT-CB) method:

− = negative, no color or light blue color.
D = doubtful, dirty blue or very pale pink color.
+S, +M, +I = positive, coral red color; reaction either slight, moderate, or intense, depending on the degree of coloration.

Reagent controls: One drop of each reagent for each method was added to separate depressions in a spot plate, mixed, and allowed to stand for

[1a] Tarshis, M. S.: Amer Rev Resp Dis, 1960, *82*, 82. [b] Tarshis, M. S.: Trans 19th Conf on Chemother Tuberc, VA-Armed Forces (in press).

[2] Gutiérrez-Vázquez, J. M.: Rev Lat Amer Microbiol, 1958, *1*, 287.

[3] Gutiérrez-Vázquez, J. M.: Amer Rev Resp Dis, 1960, *81*, 412.

[4] Tuberculosis Laboratory Methods: VA-Armed Forces Cooperative Study on the Chemotherapy of Tuberculosis, Dept. Med. & Surg., Washington, D. C., 1958, pp. 28–29.

approximately five minutes. Each mixture should be colorless under white or day light. Under ultraviolet light, however, the OT-CB mixture is photosensitive and forms an irreversible blue color which may interfere with the reading of the results. Therefore, when performing niacin tests by the OT-CB method in a bacteriologic safety hood, the ultraviolet light should not be kept on during the performance and reading of the tests.

Medium controls: From 2 to 10 drops of distilled water were added to a tube of the uninoculated medium, depending on the amount of fluid already present, and niacin tests were performed by each method on the water blanks in exactly the same manner as for the inoculated medium.

Pigmented strain controls: Pigmented strains which colored the water extracts also were compared with the following three controls: (*a*) 2 drops of extract, 1 drop of aniline reagent, and 1 drop of distilled water; (*b*) 2 drops of extract, 1 drop of *o*-tolidine reagent, and 1 drop of water; and (*c*) 2 drops of extract, 1 drop of cyanogen bromide reagent, and 1 drop of water.

All procedures were carried out under a well-

TABLE 1

COMPARATIVE RESULTS OF THE ANILINE-CYANOGEN BROMIDE AND O-TOLIDINE-CYANOGEN BROMIDE DIRECT QUALITATIVE MICRO-NIACIN TESTS AFTER INCUBATION OF CULTURES OF DIFFERENT TYPES OF MYCOBACTERIA FOR VARIOUS PERIODS ON TWEEN®-ALBUMIN NIACIN TEST MEDIUM

Strain	Test Periods								
	7 Days		10 Days		14 Days		21 Days		
	Method								
	A-CB	OT-CB	A-CB	OT-CB	A-CB	OT-CB	A-CB	OT-CB	C
Human tubercle bacilli									
A-50	+S	−	+M	D	+M	+S	+I	+I	−
A-51	+M	+S	+M	+S	+M	+M	+I	+I	−
A-52	+M	+S	+M	+S	+M	+M	+I	+I	−
A-53	+M	+M	+M	+M	+M	+M	+I	+I	−
B-1	+S	+S	+S	+S	+M	+M	+I	+I	−
B-2	+S	+S	+S	+S	+M	+M	+M	+M	−
M-1	+S	+S	+S	+S	+S	+S	+M	+M	−
M-2	+S	+S	+S	+S	+M	+M	+I	+M	−
H37Rv	+M	+S	+M	+S	+M	+M	+I	+I	−
Bovine tubercle bacilli									
Copenhagen	−	−	−	−	−	−	−	−	−
Ravenel	−	−	−	−	+S	+S	+S	+S	−
Avian tubercle bacilli									
Kirchberg	−	−	−	−	−	−	−	−	−
Sheard	−	−	−	−	−	−	−	−	−
Unclassified mycobacteria									
Photochromogens									
AP-18	−	−	−	−	−	−	−	−	−
WP-2	−	−	−	−	−	−	−	−	−
Scotochromogens									
AS-19	−	−	−	−	−	−	−	−	−
AS-20	−	−	−	−	−	−	−	−	−
Battey									
AB-2	−	−	−	−	−	−	−	−	−
RB-7	−	−	−	−	−	−	−	−	−
Saprophytic mycobacteria									
M. smegmatis-a	−	−	−	−	−	−	−	−	−
M. phlei-a	−	−	−	−	−	−	−	−	−

C = controls; − = negative; D = doubtful; +S, +M, +I = slightly, moderately, and intensely positive. *See* Methods.

A–CB = analine–cyanogen bromide method; OT–CB = *o*-tolidine–cyanogen bromide method.

ventilated bacteriologic safety hood. Each test was repeated twice. The final readings represent average results.

The data presented in table 1 summarize typical findings from each group of organisms. It may be seen that all of the human tubercle bacilli gave positive niacin tests with both methods, whereas all of the other strains, with one exception, gave negative results. The Ravenel bovine strain exhibited a slightly positive reaction with both techniques after the fourteenth- and twenty-first-day periods. As observed previously,[1] it will be noted that, as the period of incubation increased, there was a corresponding increase in both the number and degree of positive results. When used on cultures from seven to ten days old, the sensitivity of the aniline-cyanogen bromide test was slightly better than the *o*-tolidine-cyanogen bromide method. When used on older cultures, however, the sensitivity of both techniques was essentially the same.

* * *

In the *o*-tolidine-cyanogen bromide test described by Gutiérrez-Vázquez,[2,3] 0.5 to 0.8 ml. of distilled water was added to the test strain showing heavy growth on Löwenstein-Jensen medium. The culture was then autoclaved for fifteen minutes at 15 pounds' pressure, cooled in a water bath, and the extract was collected and tested.

After numerous trials by this procedure, certain limitations were noted. First, longer periods were required to obtain sufficient growth on Löwenstein-Jensen medium for performing niacin tests than on some of the other media studied.[1] Second, the procedure of autoclaving whole cultures of Löwenstein-Jensen medium resulted in the loss of some cultures from the disruption of the medium and loss of the water extracts despite all precautions to prevent this. Also, the extraction of niacin by autoclaving did not appear to be significantly greater than the extraction of niacin at room temperature. Third, once autoclaved, the cultures could no longer be used for other purposes or incubated further in the event the niacin test results were negative or doubtful. Fourth, although the method of water extraction from cultures of Löwenstein-Jensen medium has helped improve the direct qualitative method greatly, in some instances enough malachite green from the medium might get into the extracts and interfere with the reading of the results. Because of these limitations, and on the basis of previous observations,[1] it was decided to change this part of the procedure by using a medium which would permit earlier testing of organisms for niacin production with dependable results and autoclaving of the water extracts rather than the whole cultures containing the water. Experience thus far indicates that more satisfactory results can be obtained by the use of these modifications.

Although both the micro-tube and micro-swab tests described previously[1] also could be used with the *o*-tolidine-cyanogen bromide method when the color reactions were moderately to intensely positive, the micro-plate test was somewhat easier to read when the results were either doubtful or slightly positive.

In summary: An investigation was undertaken to compare two recently described direct qualitative micro-niacin tests. When used under the conditions described, these tests can be performed, in most instances, on cultures only seven to ten days old, thus reducing the testing time by approximately two to three weeks.

When used on cultures from seven to ten days old, the sensitivity of the aniline-cyanogen bromide method was slightly better than the *o*-tolidine-cyanogen bromide procedure. When used on older cultures, however, the sensitivity of both tests was essentially the same.

The Tween®-albumin niacin test medium used to culture the organisms and perform the tests was found to give not only early, eugonic, and uniform growth, but also reproducible and consistent results.

The chief advantages of both tests are simplicity, efficiency, safety, economy, and the shorter time required before performing them. They have proved useful as a screening procedure for differentiating human tubercle bacilli from other mycobacteria.

MAURICE S. TARSHIS
Medical Research Laboratory
Veterans Administration Hospital
Alexandria, Louisiana

April 27, 1960

RISTOCETIN TREATMENT FAILURE IN PULMONARY TUBERCULOSIS

Since the advent of antimicrobial agents for the treatment of tuberculosis, there has been a constant and determined effort to ascertain the value of new drugs in the treatment of the disease. In keeping with this policy, a cooperative clinical trial of ristocetin[1] in pulmonary tuberculosis was carried out at the Tuberculosis Division of the Halifax Health Centre and at the Nova Scotia Sanatorium during the year 1959.

In the former hospital, 3 patients with newly diagnosed disease and one patient with reactivated disease were treated with ristocetin, while at the Nova Scotia Sanatorium 7 patients with advanced chronic disease—all known to be resistant to the standard antituberculous drugs—were so treated. Two routes of administration were used: intravenous in 6 patients and intramuscular in 5. For intramuscular use, 0.5 gm. of crystalline ristocetin was dissolved in 5.0 ml. of saline and combined with 5 mg. of hydrocortisone sodium succinate to minimize local irritation from the drug.

As shown in table 1, 7 male and 4 female patients were included in the series, with ages ranging from twenty to eighty-six years. The sputum was positive for tubercle bacilli in all except one patient. In the 7 patients with chronic far advanced disease already referred to, the tubercle bacilli were also known to be resistant to streptomycin, PAS, and isoniazid. Cycloserine had also been given to 4 patients. Five patients were classified as having moderately advanced and 6 as having far advanced disease; bronchopleural fistulas were present in 3 patients as a persistent complication following resectional surgery.

Although, as seen in table 1, various amounts of the drug were administered, in no instance was improvement noted either clinically or roentgenographically and, in fact, actual extension of disease occurred in 2 patients.

A rather high incidence of serious complications was noted. In one instance, neutropenia was encountered after 18.5 gm. of ristocetin had been administered by the intravenous route. The leukocyte count, which was 6,900 per cu. mm. at the beginning of treatment, fell to 2,750 per cu. mm., the polymorphonuclear leukocytes dropping from 62 to 20 per cent. Bone marrow examination revealed a mild generalized hyperplasia with partial arrest of granulopoiesis at the juvenile stage. Following cessation of the drug, the leukocyte count promptly rose to 11,950 per cu. mm. and the polymorphonuclear leukocytes to 40 per cent. In 2 patients, there was a moderate fall in hemoglobin and erythrocyte count, but the leukocyte count was unaffected. In 3 cases, definite mental depression occurred; one 50-year-old patient threatened to commit suicide. Finally, a 48-year-old female patient suffered from severe exfoliative dermatitis and was acutely ill for several days after having received a total of 24 gm. of ristocetin intramuscularly.

No beneficial effect was noted from the concomitant use of hydrocortisone sodium succinate, which did not significantly affect the occurrence of local pain, tenderness, or swelling. A moderate number of *in vitro* susceptibility tests to ristocetin of tubercle bacilli from each patient were performed throughout the course of the study. In all cases, the tubercle bacilli were reported as "resistant" or "slightly susceptible" to the antimicrobial.

In summary: Ristocetin was used on a trial basis in 11 patients with pulmonary tuberculosis: 4 new cases and 7 in which treatment by other means had previously been ineffective. The dosage regimen was 1.0 gm. daily for three months. The drug was ineffective in all instances. Complications were frequent and included one case of neutropenia, two of mild anemia, three of marked depression, and one of severe exfoliative dermatitis.

It is concluded that ristocetin is of no value in the treatment of tuberculosis; and that, even in low daily dosage, it would be prohibitively toxic in long-term treatment regimens.

HELEN HOLDEN[2]
Nova Scotia Sanatorium
Halifax, Nova Scotia
S. J. SHANE
Halifax Health Centre, Tuberculosis Division; and Department of Medicine, Dalhousie University
Halifax, Nova Scotia
C. E. VAN ROOYEN
Department of Bacteriology, Dalhousie University
Halifax, Nova Scotia

May 31, 1960

[1] Ristocetin (as Spontin) was provided by the Abbott Laboratories, Montreal, Canada, through the courtesy of Dr. Peter Nash.

[2] After completion of the present study, a paper came to the attention of the writers entitled "The *in Vivo* and *in Vitro* Activity of Ristocetin upon *M. Tuberculosis*" by G. Spina and associates (Ann Ist Forlanini, 1958, *18*, 409). The present findings do not support the suggestion of those writers that a human trial of ristocetin in tuberculosis is likely to be of value.

TABLE 1

DATA ON PATIENTS IN STUDY OF RISTOCETIN THERAPY

Patient Number	Sex	Age	Sputum	Extent	Result	Dose	Route	Total Grams	Complications
1	M	40	Positive for *M. tuberculosis*	M.A.*	Unchanged	0.5 gm. b.i.d.†	I.V.‡	87	None
1	M	20	Negative for *M. tuberculosis*	M.A.	Unchanged	0.5 gm. b.i.d.	I.V.	18	Neutropenia
3	M	37	Positive for *M. tuberculosis*	M.A.	Unchanged	1.0 gm. daily	I.M.	7	Extreme pain at site of intramuscular injections
						0.5 gm. b.i.d.	I.V.	91	
4	M	43	Positive for *M. tuberculosis*	M.A.	Unchanged	0.5 gm. b.i.d.	I.V.	72	None
5	F	41	Positive for *M. tuberculosis*	F.A.	Worse	0.5 gm. b.i.d.	I.V.	73	Depression
6	M	57	Positive for *M. tuberculosis*	F.A.	Unchanged	0.25 gm. b.i.d.	I.M.	63	None
7	F	27	Positive for *M. tuberculosis*	F.A.	Unchanged	0.5 gm. b.i.d.	I.V.	93	None
8	F	86	Positive for *M. tuberculosis*	M.A.	Worse	0.5 gm. b.i.d.	I.M.	25	(1) Depression (2) Fall in hemoglobin and erythrocyte count
9	M	50	Positive for *M. tuberculosis*	M.A.	Unchanged	0.5 gm. b.i.d.	I.M.	62	Depression
10	M	60	Positive for *M. tuberculosis*	F.A.	Unchanged	0.5 gm. b.i.d.	I.M.	28	Fall in hemoglobin and erythrocyte count
11	F	48	Positive for *M. tuberculosis*	F.A.	Unchanged	0.5 gm. b.i.d.	I.M.	14	Exfoliative dermatitis, severe

* M.A.—moderately advanced; F.A.—far advanced

† b.i.d.—twice a day

‡ I.V.—intravenously; I.M.—intramuscularly

Correspondence

SICKLE CELL TRAIT AND TUBERCULOSIS

To the Editor of the American Review of Respiratory Diseases:

Ryan, O'Connor, McCurdy, and Katz[1] published a paper entitled "Sickle Cell Trait and Tuberculosis" in the April, 1960, issue of the REVIEW. Their paper refers to a "*dispute*. . . over the incidence of sickle cell trait among Negro tuberculous patients." Weiss and Stecher[2] presented data in 1952 which indicated that the sickle cell trait was more common in tuberculous Negroes (12.6 per cent) than in *nontuberculous* Negroes *admitted to the same hospital* (5.3 per cent). The difference was small but statistically significant.

Dr. Ryan and his associates present data which do not support ours. The difference may be explained by the fact that the data in Ryan's investigation were not collected in a fashion comparable to ours.

Our study was carried out with concurrent controls known to have normal chest films at the time of the study and not restricted as to age, race, or sex. All patients were admissions to a large municipal general hospital in 1951. Dr. Ryan's controls consisted of pregnant females not further described. Therefore, it cannot be denied that unknown factors might have been operative in his study in such a way as to reduce the difference in the sickle cell prevalences between his tuberculous group and his controls. In fact, we did not compare the prevalence of the sickle cell trait among tuberculous Negroes with the prevalence in the *general population*, as Ryan and associates allege. Our controls were a rather specific segment of the population. Furthermore, the reported prevalence of the sickle cell trait in pregnant females is not as consistent as Ryan and associates would have us believe.[3]

Ryan and associates say that "The unusually low figure for the incidence of the sickle cell trait in their 'control group' is evidence that their conclusions were derived from the study of too small a sample," in referring to our work. A statement of this sort is incorrect Aristotelian immediate inference because the conclusion does not necessarily follow from the premise.

Dr. Ryan and his associates state that there was no difference as to type of tuberculosis among tuberculous patients with the sickle cell trait compared with those without the trait. We found a difference. However, it should be carefully noted that Ryan and associates investigated *extent* of pulmonary tuberculosis while we investigated the prevalence of *exudative* types of pulmonary tuberculosis. We clearly defined the term "exudative" in a footnote and even illustrated the definition with 4 well-reproduced chest films.

Further, we presented figures on the prevalence of fever on admission and of duration of tuberculous symptoms prior to admission to support the idea that tuberculous patients with the sickle cell trait tend to have a more acute and toxic form of pulmonary tuberculosis than do tuberculous Negroes without the sickle cell trait. Acuteness and toxicity are characteristic of exudative tuberculosis.

Ryan and associates presented no data on these aspects of the problem and yet concluded that "There is nothing noted in the disease pattern of tuberculosis as it occurs in patients with sickle cell trait to distinguish it from the disease in patients without the trait." In view of the limitations of their analysis, this is a remarkably dangerous generalization.

Exactly the same criticisms apply to the paper by Rosenblum and co-workers,[4] cited by Ryan and associates as the only other study on this subject although there are other studies.[5] It is unfortunate that some readers of the paper by Ryan and associates will assume that the work of Weiss and Stecher cannot be corroborated by others. This may be true but has not yet been demonstrated.

Actually there is no dispute. There are different sets of data collected at different times in different ways and under different conditions.

WILLIAM WEISS
Philadelphia General Hospital
34th Street and Curie Avenue
Philadelphia 4, Pennsylvania

July 12, 1960

[1] RYAN, T. J., *et al.*: Amer Rev Resp Dis, 1960, *81*, 546.

[2] WEISS, W., AND STECHER, W.: AMA Arch Int Med, 1952, *89*, 914.

[3] ADAMS, J. Q., *et al.*: Obstet Gynec (NY), 1953, *2*, 335.

[4] ROSENBLUM, R., *et al.*: AMA Arch Int Med, 1955, *95*, 540.

[5] VANDEPITTE, J., *et al.*: Ann Soc Belg Med Trop, 1953, *33*, 259.

RELIABILITY OF THE NIACIN TEST: THE ORIGINAL KONNO DIRECT TEST

To the Editor of the American Review of Respiratory Diseases:

In your journal of September, 1960, Dr. Konno, in a letter to the Editor, implies that our studies,[1] on the reliability of the niacin test for distinguishing between human tubercle bacilli and other mycobacteria, differ markedly from those obtained by other investigators. On behalf of my associates and myself I would like to take this opportunity to clarify our position. It appears that Dr. Konno did not appreciate that we were referring to his original description of the Konno direct qualitative test for niacin production, exclusively.[2] Despite the fact that we were unable to confirm Dr. Konno's observations on the original description of his direct test, we do agree with Dr. Konno on the reliability and sensitivity of the modified procedure, of the Konno direct qualitative test, as recently described by Runyon and his associates.[3]

In retrospect, I would like to re-emphasize that our conclusion that the original Konno direct qualitative test for niacin production is unreliable for differentiating *M. tuberculosis* from other acid-fast bacilli is based solely on our experience with this specific procedure, as originally described by Dr. Konno in the AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES, 1958, *77*, 669. The mere fact that the original Konno direct qualitative test required modification to enhance the validity of its reliability speaks for itself.

MARIE L. KOCH
Clinical Laboratory Service
Veterans Administration Center
Wood, Wisconsin

July 20, 1960

[1] KOCH, M. L., AND KROLL, A. W.: Amer Rev Resp Dis, 1960, *81*, 108.

[2] KONNO, K., *et al.*: Amer Rev Tuberc, 1958, *77*, 669.

[3] RUNYON, E. H., *et al.*: Amer Rev Resp Dis, 1959, *79*, 663.

Books

THE ECOLOGY OF HUMAN DISEASE. By Jacques M. May. Pp. 327, MD Publications, Inc., New York, 1959. Price, $7.50.

This book is the first of a trilogy concerned, in the words of the author, "with some of the most important transmissible, degenerative and behavioral disorders." The seven introductory chapters of the present volume, together with the Preface, set forth the author's definitions of ecology and disease and develop his concept of the environmental factors in the human host-parasite relationship.

Dr. May's definition of disease from the ecologic point of view is "that alteration of living tissues that jeopardizes their survival in their environment." Environmental factors of relevance to human disease are discussed as three types of stimuli (inorganic, organic, and socio-cultural), and in terms of factors that condition the response of the tissues to the stimuli. The author lays much of the conditioning to genetic factors, although psychologic changes are considered, largely in the framework of Pavlovian "conditioned reflexes." Cultural factors are primarily interpreted as aspects of man's physical reaction to his environment: what it does to him in his particular society and what he has done to it.

Perhaps too great emphasis is placed on a search for "specific" environmental factors. In the introductory pages, one finds neglected the impact of information theory on current biologic thought; man remains contained in a Hegelian world, viewed more as a tissue in the internal milieu of Claude Bernard than as a cybernetic creature responding primarily to patterns of energy during his life cycle rather than to its gross quantitative variations.

The author's introductory approach, however, is appropriate to the bulk of the book's contents. Following 34 pages of introduction, there appear 264 pages of well-tabulated data concerning eleven microbial and four parasitic diseases. These are each considered from the points of view of the geographer, historian, and clinician. Attention is paid in each case to the agent, the host, transmission of the agent, and to its distribution. Detailed summaries of prevalence by country appear in most chapters, accompanied by tables and, in many instances, elaborate disease maps. Discussions of climatologic, cultural, and geographic features pertinent to each microbial or parasitic infestation provide the most interesting reading. Unfortunately, the mass of data present under each heading must perforce read in catalogue manner due to sheer quantity, but most chapters are ended by more pithy conclusions.

For the thirteen chapters dealing with individual disease topics, separate bibliographies ranging from 13 to 130 (mean 62) items are presented. It is to be regretted that no bibliography appears for the seven introductory chapters.

As set forth herein, Dr. May's ecologic concept of human disease appears to remain that of the twentieth century cartographer, and he presents voluminous data to document his point of view. One awaits his subsequent volumes with curiosity, particularly the third with its promise to move from the transmissible to the degenerative and behavioral diseases, areas in which his methodology may reach more rocky soil.

WILLIAM N. CHRISTENSON
Department of Medicine
The New York Hospital
New York, New York

LE CATHETERISME DU COEUR DROIT ET DES ARTERES PULMONAIRES EN PNEUMOLOGIE. By Pierre Trocme and Jacques Chedal. Pp. 110, Masson et Cie, Paris, 1958. Price, 1,600 Fr.

This paperback book is a short account of the authors' experiences with the technique of cardiac catheterization as applied to the study of the pulmonary circulation in a variety of disorders of the lungs. After a brief description of the technique of catheterization, the equipment employed, the treatment and interpretation of the data obtained, the authors present their observations on patients with unilateral bronchial obstruction and hypoventilation, asthma, emphysema, chronic bronchitis, pneumonoconiosis, bronchiectasis, and cor pulmonale. Although these observations are interesting, they often consist of no more than measurements of pulmonary vascular pressures and arterial oxyhemoglobin saturation, and do not differ substantially from many similar observations available in the world literature.

The book occupies an unfortunate position with regard to its utility. As an investigative effort, the extent of the data is sharply limited, and permits only limited conclusions to be drawn. As a summary of knowledge concerning the pulmonary circulation, it is too brief and cursory to be adequate.

A few errors and inconsistencies are apparent.

As examples: units for arteriovenous blood oxygen difference in the Fick principle and for vascular resistance are incorrect; gravity is neglected in the formula for kinetic energy; in the bibliography the titles of some of the English and American references are given in English, whereas others are given in French.

DANIEL S. LUKAS
Department of Medicine
The New York Hospital-
Cornell Medical Center
New York, New York

ANTIBIOTICS ANNUAL 1959–1960. Edited by Henry Welch and Felix Marti-Ibanez. Pp. 1034, Antibiotica, Inc., New York, 1960. Price, $15.00.

This volume contains the Proceedings of the Seventh Annual Symposium on Antibiotics held in Washington, D. C., in November, 1959. Dr. Henry Welch was the chairman of this meeting and Dr. Felix Marti-Ibanez the editorial director. One cannot peruse this collection of papers without reflecting upon the recent investigations in Washington directed by Senator Kefauver which seriously questioned the objectivity of the editors of this book. An account by John Lear of the Washington hearings and the circumstances which led to them may be found in the *Saturday Review*, issue of July 2, 1960.

About 150 scientific papers, transcripts of two symposia, and four addresses concerning the challenge of new drugs are introduced by Dr. Marti-Ibanez in his characteristically pretentious style. Dr. William Bean has critically debunked the writings of Dr. Marti-Ibanez in a devastating review written in the *Archives of Internal Medicine* (1959, *104:* 839–840) and thereby, in this writer's opinion, performed a noteworthy service.

Despite all of this, there are many papers of merit recorded in this symposium which deserve comment. Outstanding is the paper of Dr. Maxwell Finland outlining the challenge of new drugs to the clinical investigator. Dr. Finland takes up a number of issues which have plagued clinical investigators for some time. One is the problem of whether or not to use a medicament which has not been shown to be effective simply because it has been shown to do no harm and may possibly do some good. Another is how to evaluate "testimonials" of allegedly brilliant successes attributed to a particular preparation which give no reference to similar cases in which the agent appeared to be worthless. Finally, he points out the tremendous gap which exists between the number and variety of new and improved drugs available for clinical trials and the grossly inadequate number of places providing facilities for their proper assessment. He recommends the establishment and support of departments of clinical pharmacology which will provide the training and talent to assess these drugs. Perhaps it may be added that many of the new products should not have been placed on the market in the first place, and that more restraint on the part of the manufacturers could lessen the number of preparations that require clinical evaluation.

A number of reports on new drugs and modifications of older preparations are presented in this symposium. Among these are colistin, a new Japanese product with properties remarkably similar to the polymyxins, potassium (alpha phenoxy ethyl) penicillin, pyrrolidinomethyl tetracycline, demethylchlortetracycline, and furaltadone, a nitrofuran with less promise, according to the paper of McCabe and associates, than the advertisements seem to indicate. New work on some of the older preparations such kanamycin, ristocetin, oleandomycin, and amphotericin is also presented.

No truly new drug of major importance was added to the therapeutic armamentarium at this meeting. Perhaps the era of the rapid introduction of important new antimicrobials is coming to a close, and we are now witnessing a mopping-up operation. If this be so, even greater responsibility is called for on the part of those entrusted with the use of antimicrobials, to employ them skillfully, to clearly recognize when a real advance has been made, and to guard against the artful promotion of products which are not of established merit.

CALVIN M. KUNIN
Department of Preventive Medicine
University of Virginia
School of Medicine
Charlottesville, Virginia

INFECTIOUS DISEASES OF CHILDREN. By Saul Krugman and Robert Ward. Pp. 340, C. V. Mosby Company, St. Louis, 1958. Price, $10.00.

In only about 300 pages, the authors discuss most infectious diseases of viral and bacterial etiology encountered among children residing in the temperate zone. The book does not cover tuberculosis, spirochetal diseases, mycoses, or animal parasites (except toxoplasma), but emphasizes the more common conditions which might be encountered by a physician in his daily practice. Thus, the authors describe, among others, the illnesses caused by the ECHO, coxsackie, and adenoviruses, hepatitis, the croup syndrome, Salmonella, and staphylococcal infections, as well as the classical contagious diseases.

The discussion of each disease is lucid and

concise, yet complete with specific comments on etiology, diagnosis, therapy, and appropriate control measures. The wide personal experience of the writers contributes not only a wealth of practical information, but also assures a well-balanced, up-to-date, and authoritative presentation. Schematic drawings and diagrams illustrate typical findings for each illness and emphasize the important differential features; photographs, many in color, show some of the important lesions. A well-chosen bibliography lists the pertinent references for each subject discussed, providing the opportunity for further study.

This volume can be recommended as one of the "basic books" which every physician dealing with children should have within easy reach. It should also prove valuable to medical students and to individuals concerned with preventive medicine.

Heinz F. Eichenwald
Department of Pediatrics
The New York Hospital-
Cornell Medical Center
New York, New York

The Mediastinum. By Tom F. Leigh and H. Stephen Weens. Pp. 246, Charles C Thomas, Springfield, Illinois, 1959. Price, $11.50.

This monograph deals with the roentgenography of mediastinal diseases but, in view of the diagnostic importance of the roentgenogram in this area, it is of general interest to all physicians dealing with diseases of the chest. The initial chapters are concerned with normal roentgenographic anatomy, and include a short discussion of the distribution and inter-relationships of the several groups of intrapulmonary lymphatics. The remainder of the book consists of brief chapters reviewing categories of mediastinal lesions. Completeness of coverage can be inferred from the number of chapters, thirty in all. The greater part of the book consists of discussion of tumors separated by tissue of origin. Other chapters treat mediastinal infection, mediastinal emphysema, hemomediastinum, enterogenous cysts (several chapters), esophageal diverticulae, diaphragmatic hernias, and lesions of the aorta and branches, of the pulmonary artery, and of the superior caval system. The discussions, in keeping with the purpose of a monograph such as this, are quite brief, being little more than a discussion of the large number of illustrative roentgenograms and diagrams. The films seem generally of good quality, and in every instance the point being discussed in the text is discernible in the illustration, a situation rare enough in chest roentgenographic reproduction. References have been carefully chosen and are themselves a valuable compilation. Controversial areas have been avoided, and the authors (both professors of radiology at Emory University Medical School) write in a clear, pleasant, and authoritative fashion. Since a good part of the 246 pages is given over to illustrations, the book can be read in an evening with, in the opinion of this reviewer, a lot of pleasure and profit.

Roger M. Des Prez
Department of Medicine
The New York Hospital-
Cornell Medical Center
New York, New York

American Thoracic Society

Medical Section of the National Tuberculosis Association

Bacteriologic Considerations in the Therapy of Chronic Suppurative Bronchitis and Bronchiectasis

A Statement of the Committee on Therapy

Chronic bacterial infections of the bronchi are increasing in importance in spite of major advances in treatment of acute bronchopulmonary infections. This statement is concerned with certain bacteriologic considerations in the treatment of such infections. The term chronic suppurative bronchitis refers to any chronic inflammatory bronchial disease with significant purulent sputum in which such specific conditions as tuberculosis, mycotic infections, lung abscess, and neoplasms have been excluded. Although bronchiectasis may differ in its pathogenesis from chronic bronchitis and often requires surgical treatment, the bacteriologic considerations are similar.[1] These infections take on special significance when they occur in patients whose pulmonary function is decreased. Here, bronchial infection contributes significantly to the morbidity and mortality from pulmonary and cardiac failure.

The control of chronic infections in the bronchi is difficult for several reasons. The very structural and functional abnormalities that predispose to infection also interfere with the drainage so essential to successful therapy and make it difficult to deliver adequate concentrations of therapeutic agents to the site. The exact identification of the pathogenic bacteria is difficult and often impossible. It should be emphasized that antibacterial therapy must be used in conjunction with other measures if maximal benefit is to be achieved. Bronchial drainage and antibacterial therapy are interdependent, since control of infection is impossible without good drainage and since drainage is improved when bronchial edema and congestion respond to antimicrobial drugs.

Although there is a need for further systematic and controlled study of various antibacterial agents in chronic bronchopulmonary suppuration, we may nevertheless take advantage of much that is known in establishing a basis for effective therapy.

The bacteriology of chronic bronchial infections: A large amount of careful investigation, particularly by British workers, has led to a better understanding of the bacterial patterns encountered in those diseases under discussion here. From these studies, certain facts seem both clear and pertinent:

(*1*) The bronchial tree in normal individuals is essentially free from bacteria, and one feature common to virtually all forms of chronic bronchitis is the invasion of the bronchial tree by common mouth flora.

(*2*) The most frequently isolated bacteria other than common mouth flora in untreated suppurative bronchitis are *Hemophilus influenzae* and *Diplococcus pneumoniae*. Other pathogens less often encountered are *Staphylococcus aureus*, certain Klebsiella species, and Group A. hemolytic streptococci. The presence of these organisms can be shown to correlate with clinical exacerbations and increase in purulent sputum (1, 2).

(*3*) Certain gram-negative bacteria (*Pseudomonas aeruginosa*, Proteus species, Klebsiella-aerobacter species, *Escherichia coli* and related species) may occasionally be responsible for serious bronchial infections. However, these organisms more commonly appear following chemotherapy and are by no means always associated with worsening of the patient's condition or with return of purulent sputum (3, 4).

(*4*) Fusospirochetal organisms (5), members of the bacterioides group, and anaerobic streptococci (6) may cause serious bronchial infections. These anaerobic organisms are not easily cultured and are not found with routine culture techniques.

(*5*) It is important to appreciate the sampling errors encountered in attempting to isolate potential pathogens from sputum. Multiple sampling and sampling of digested or homogenized sputum specimens increases the yield, but still may fail to reveal known pathogenic organisms even when there is clear evidence of active infection (1).

Indications for antibacterial therapy: The indications for therapy in chronic bronchial infection are not always clear. From what has already been said, it is obvious that one cannot depend solely on sputum cultures in establishing criteria for starting antimicrobial drugs. It is also well known that, in patients with chronic pulmonary insufficiency, severe respiratory and cardiac failure may

[1] Antibacterial therapy is not to be regarded as a substitute for resection of localized bronchopulmonary disease. Preoperative control of infection, however, improves the results of resection for bronchiectasis.

be precipitated by an increase in bronchial infection without such systemic manifestations as fever and leukocytosis (7). While these signs of infection should no more be disregarded than should the finding of pathogenic bacteria in the sputum, the decision to use antibacterial drugs may be necessary in their absence. Grossly purulent sputum in patients known to have bronchitis and bronchiectasis is, with few exceptions, an indication of infection. However, eosinophils in large numbers may give the appearance of pus. Examination of the sputum smear stained by Wright's method enables one to differentiate purulence due to infection from that due to allergy.

Choice of antimicrobial drugs: Ideally, the choice of antimicrobial drugs should be based on knowledge of the etiologic agent and its susceptibility to the various drugs. Even with the best of laboratory facilities this is not always possible, since culture of the sputum may fail to reveal all of the important pathogens. When *H. influenzae* is isolated, its growth characteristics are often such as to make accurate determination of antimicrobial susceptibility impossible. It is therefore necessary in many instances to make the choice of antimicrobial drugs at least partially on the basis of probabilities. Nevertheless, with a knowledge of the common bacterial patterns outlined above, an intelligent choice should be possible.

The predictable effectiveness of penicillin against pneumococci and certain of the important anaerobes, plus the fact that in high concentrations it may also affect *H. influenzae*, make this one of the most valuable drugs in treating bronchopulmonary infections. Penicillin has the advantage of being bacteriocidal, it is relatively inexpensive, and high blood and tissue levels can be attained. The use of the aerosol form of this antimicrobial is not recommended because of the danger of producing hypersensitivity and the lack of demonstrated effectiveness. Blood levels with oral penicillin and with procaine penicillin intramuscularly are unpredictable and, therefore, the use of frequent injections of aqueous crystalline penicillin is recommended as initial therapy. Since penicillin will not produce maximal response in some cases of chronic bronchial infections (8), a combination of penicillin and tetracycline is preferred. This will provide effective therapy for a broader spectrum of bacteria, including *H. influenzae*. Chloramphenicol may be used in place of tetracycline, but its hematopoietic toxicity calls for caution in its repeated and prolonged administration. It seems advisable to reserve chloramphenicol for those instances in which factors such as susceptibility tests clearly show its superiority. Streptomycin is probably inferior to the tetracyclines against *H. influenzae*, and it too should be reserved for instances in which there are specific indications for its use. Sulfonamides in adequate dosage may be useful.

When it is suspected that one of the gram-negative bacilli or *Staphylococcus aureus* is the principal pathogen, the intelligent choice of antimicrobials can be made only on the basis of susceptibility tests. In such instances, when the organisms are resistant to all other agents, polymyxin and neomycin may be given as aerosols (9). The risks of renal toxicity are markedly reduced by using this route of administration.

Initial intensive therapy: When bacterial infection of the bronchi contributes to severe pulmonary or cardiac failure, hospitalization is required for the prompt control of infection and institution of other therapeutic measures. Even in less serious situations, hospitalization allows for administration of adequate doses of antimicrobials at frequent intervals. Better sputum specimens for culture can be obtained and therapy better supervised. Daily measurements of sputum volume, estimates of degree of purulence, and frequent sputum smears and cultures should be done in order to judge the effectiveness of the therapy and need for changes in therapeutic agents. Bronchial drainage (by the use of bronchodilator-decongestant therapy, expectorants, humidification, respiratory assistance, and postural drainage) should be used in conjunction with antibacterial agents, and supervision of these measures can best be accomplished in the hospital. The goal of antibacterial therapy should be the reduction of sputum volume and purulence to a minimum. Effective dosages of antimicrobial drugs combined with the other measures mentioned above accomplish this goal in the majority of cases within seven to ten days.

Continuous or prophylactic therapy: Even with the best results from the intensive treatment of chronic bronchial infections, recurrence of infection is usual. Continuous efforts to promote drainage undoubtedly help to delay the return of infection, but all too often the period of freedom from infection is short lived. The tetracyclines have been used in an attempt to suppress chronic infection and prevent acute bacterial exacerbation (10–13), but the effectiveness of such therapy is often insufficient to justify the expense involved. Two important points should be made, however, in connection with this approach. Most patients tolerate prolonged or repeated use of the tetracyclines in small doses and usually do not develop

significant infections with resistant bacteria and fungi. It would seem logical that any long-term use of antimicrobials would be more effective if initiated when the patient has been made as free from infection as possible by intensive therapy.

THOMAS B. BARNETT
BENJAMIN BURROWS
EDWARD DUNNER
JOHN R. DURRANCE
ATTILIO D. RENZETTI, JR.
HERBERT SCHMIDT
WILLIAM W. STEAD
DONALD L. PAULSON, *Chairman*

REFERENCES

(1) MAY J. R.: The bacteriology of chronic bronchitis, Lancet, 1953, *2*, 534.
(2) STUART - HARRIS, C. H., POWNELL, M., SCOTHORNE, C. M., AND FRANKS, Z.: The factor of infection in chronic bronchitis, Quart J Med, 1953, *22*, 121.
(3) ELMES, P. C., KNOX, K., AND FLETCHER, C. M.: Sputum in chronic bronchitis, Lancet, 1953, *2*, 903.
(4) BARNETT, T. B., AND CROMARTIE, W.: Unpublished data.
(5) SMITH, D. T.: Etiology of primary bronchiectasis, Arch Surg, 1930, *21*, 1173.
(6) BENSTEAD, J. G.: Flora of 100 bronchial secretions with particular reference to anaerobic cocci, Lancet, 1950, *1*, 206.
(7) STONE, D. J., SCHWARTZ, A., NEWMAN, W., FELTMAN, J. A., AND LOVELOCK, F. J.: Precipitation by pulmonary infection of acute anoxia, cardiac failure and respiratory acidosis in chronic pulmonary disease, Amer J Med, 1953, *14*, 14.
(8) DOUGLAS, A. C., SOMNER, A. R., MARKS, B. L., AND GRANT, I. W. B.: Effects of antibiotics on purulent sputum in chronic bronchitis and bronchiectasis, Lancet, 1957, *2*, 214.
(9) SPINK, W. W.: Clinical problems relating to the management of infections with antibiotics, JAMA, 1953, *152*, 585.
(10) MCVAY, L. V., JR., AND SPRUNT, D. H.: Antibiotic prophylaxis in chronic respiratory diseases, AMA Arch Intern Med, 1953, *92*, 833.
(11) MEDICAL RESEARCH COUNCIL—Subcommittee of the Antibiotics Clinical Trials: Brit Med J., 1957, *2*, 255.
(12) ELMES, P. C., FLETCHER, C. M., AND DUTTON, A. A. C.: Prophylactic use of oxytetracycline for exacerbations of chronic bronchitis, Brit Med J, 1957, *2*, 1272.
(13) HELM, W. H., MAY, J. R., AND LIVINGSTON, J. L.: Long-term oxytetracycline therapy in advanced respiratory infections, Lancet, 1954, *2*, 630.

The Use of Respirators in the Treatment of Chronic Pulmonary Emphysema

A Statement of the Committee on Therapy

It has been established that mechanical resuscitators can be of life-saving importance in the management of patients who are rapidly asphyxiated as a result of suffocation or respiratory paralysis. The results of physiologic study make it apparent that such mechanical devices may be equally important to patients with acute and chronic diseases of the chest. The basic physiologic indication for the use of such apparatus, namely, inadequate alveolar ventilation, is no different in the latter diseases than in the former but, because of a less rapid onset and progression of symptoms, its recognition may be more difficult.

A common clinical setting in which artificial ventilation is used today is in the patient with advanced chronic pulmonary emphysema. Such patients, frequently in a state of chronic carbon dioxide retention and hypoxemia, suffer a new insult to their respiratory reserve if bronchial infection, chest trauma, heart failure, et cetera, occur. This added insult may lead to a decrease in alveolar ventilation and, hence, to further hypoxemia and to an elevation of arterial carbon dioxide which may reach narcotic levels. A recent history of increasing somnolence or decreasing mental alertness may also serve as a clue to impending carbon dioxide narcosis in chronically disabled individuals. The presence of polycythemia and/or heart failure in chronic pulmonary disease should lead the physician to suspect the possibility that excessive blood carbon dioxide tension is present or may occur. Of great importance is the recognition that the administration of narcotics, sedatives, and oxygen (without the use of mechanical assistance) may induce hypercapnia in any such patients. The laboratory confirmation of this diagnosis is best made by a measurement of the arterial carbon dioxide tension. However, in the absence of any evidence for metabolic alkalosis, an elevation of venous blood–carbon dioxide content, together with an acid urine, offer a less precise but acceptable clinical laboratory confirmation. When carbon dioxide narcosis has been diagnosed, mechanical respiratory assistance is frequently indicated. The aim of using a device for artificially providing adequate alveolar ventilation is the correction of hypoxemia and the restoration of the arterial carbon dioxide tension to a non-narcotic level until time has elapsed for other measures to improve pulmonary ventilation. The adequacy of ventilatory assistance of this type of therapy is best judged by determination of arterial CO_2 tension.

The mechanical devices available for use in the aforementioned circumstances are of two general types, namely, those which provide intermittent inspiratory positive pressure through the airways and those which act to expand the thoracic cavity by external means, such as a body respirator. The intermittent positive pressure devices require an initial inspiratory effort on the part of the patient to cycle the machine unless an automatic cycling device is used. Such devices are available for all machines and should be used for the apneic patient and patients with decreased ventilatory drive. The body respirators are of two general types: those which attempt to encase the anterior thorax and abdomen (cuirass type) and those which encase the whole body (tank type). In general, the cuirass type has been found to be ineffective for use in patients with impaired ventilatory mechanics, such as individuals with chronic pulmonary emphysema.

The choice between the two general classes of respirators, that is, the intermittent positive pressure breathing apparatus (IPPB) or the tank type, is a highly individualized matter. In some patients who require prolonged assisted respiration, such as the comatose or semi-stuporous patient, the use of IPPB instruments with a tracheostomy with a leak-proof cuff provides satisfactory levels of alveolar ventilation. The use of a tank respirator in the presence of a tracheostomy often requires a special type of airway connector, particularly if the patient's neck is short.

It cannot be emphasized too strongly that sequential analysis of arterial blood gases is necessary for judging the adequacy of prolonged respiratory assistance. Further, when being used in seriously ill patients, it is recommended that twenty-four-hour care should be carried out by personnel instructed in the operation of the given resuscitator. With those respirators which are capable of automatic cycling, it may at times be desirable to administer sufficient depressant medication to allay anxiety and increase patient acceptability. This should never be done until it is certain that the respirator is performing satisfactorily. It is recommended that the inspired oxygen concentration be well under 100 per cent because of the demonstrated hazards of continuous administration of 100 per cent oxygen and because com-

plete arterial hemoglobin saturation with oxygen can almost always be achieved in patients with alveolar hypoventilation when lesser concentrations of oxygen are administered. In some patients undergoing artificial ventilation, the development of hypokalemic hypotension and gastric distention has been noted. It is therefore important that cognizance be taken of these complications.

The question of the use of artificial respirators at frequent intervals by patients with chronic hypoxemia and hypercapnia at home or in institutions for chronic care is a controversial one. Before recommending the use of such equipment on a wide scale it would appear that objective data are needed on the natural history of chronic pulmonary emphysema. Some patients with severe chronic pulmonary disease can maintain relatively stable blood-gas concentrations for periods of years by the use of commonly accepted measures such as bronchodilators, expectorants, intermittent voluntary deep breathing, et cetera. In some patients, arterial carbon dioxide tension may be normal while in others it may be chronically elevated without apparent deleterious effects. It has been shown that the application of intermittent positive pressure alone is of little value to such chronically disabled individuals, but that it may offer a certain advantage in the administration of aerosolized medication.

In summary, respirators may be life saving in the management of acute or subacute illnesses which diminish the respiratory reserve of individuals already suffering from chronic respiratory disability. Presently available information does not support an indiscriminate use of this type of equipment for the relatively "stable" phases in such patients even in the presence of chronic CO_2 retention.

THOMAS B. BARNETT
BENJAMIN BURROWS
EDWARD DUNNER
JOHN R. DURRANCE
ATTILIO D. RENZETTI, JR.
HERBERT SCHMIDT
WILLIAM W. STEAD
DONALD L. PAULSON, *Chairman*

Use of Aerosolized Medication in Bronchopulmonary Diseases

A Statement of the Committee on Therapy

The use of inhalation as a route for the administration of therapeutic agents to patients with bronchopulmonary disease has become widespread in recent years. The appreciation of the importance of providing moisture to the respiratory tract and the use of detergents have served to increase the applications of aerosol therapy. The basic premise in the employment of this form of therapy has been that a given therapeutic agent may achieve the desired result by inhalation more effectively and with less extrapulmonary action than by the oral or systemic routes. The purpose of this statement is to evaluate the evidence for this premise and the clinical experience with this form of therapy.

The aim of inhalation therapy is to deliver a therapeutic agent directly to the site of desired action. It is known that droplet nuclei of a critical range of size (0.5 to 3.0 μ) must be suspended in air in order to be deposited in the finer radicals of the bronchial tree. Several commercially available nebulizers can produce droplets in this size range. The therapeutic agents often administered by this route are: (*1*) sympathomimetic drugs, (*2*) detergents, (*3*) proteolytic enzymes, (*4*) antimicrobial drugs, and (*5*) humidified air.

Successfully administered aerosol therapy requires careful attention to properly controlled breathing techniques during aerosolization since the nebulized agents are carried in the inspired air and thus tend to be carried to the better ventilated portions of lung. Whereas bronchodilator and wetting agents are used for the purpose of achieving maximal opening of the bronchial tree and the clearing of secretions, the only manner in which wide dispersion of the aerosol can be accomplished is by careful attention to a *slow, deep* pattern of breathing. Herein lies the greatest advantage perhaps of intermittent respiratory positive pressure which encourages this type of breathing.

There is little doubt that epinephrine and related drugs are useful as bronchodilators and decongestants in many patients with acute and chronic bronchial disease. It has been demonstrated further that inhalation is the preferred route of administration to such patients, since by this route desirable results are achieved with small doses and fewer undesirable side effects. The subcutaneous administration of epinephrine preparations may provide a rapid and effective result in a patient having an acute attack of allergic bronchial asthma. In situations characterized by the production of large quantities of thick, tenacious mucus, the combination of bronchodilators, wetting agents, and humidification by aerosol provides important assistance in evacuating the obstructing secretions.

Before discussing the use of detergents, it should be pointed out that adequate hydration of a patient and his secretions, not only by the inhalation route but also by the oral or systemic route, is of prime importance when a decrease in the viscosity of bronchopulmonary secretions is desired. Detergent aerosols have now been used for some time in an attempt to aid patients to expectorate bronchial secretions. It should be remembered that detergents are not mucolytic; their action depends primarily on the physical property of lowering surface tension. This action theoretically may lead to penetration of water into viscous masses of sputum, thereby increasing their water content and lowering their viscosity. It is also likely and perhaps more important that this surface tension action helps to dislodge masses of mucus from the bronchial epithelium and aids in their elimination. Although many clinicians have the impression that the detergent solutions commercially available do, in fact, aid in eliminating secretions, no well-controlled study has demonstrated this. Moreover, the addition to a detergent of substances known to produce a serous discharge (such as iodides) makes evaluation of the detergent action itself more difficult. Since, except for occasional minor local irritation, no serious toxicity results from their use, it can at least be said that the detergent aerosols in concentrations less than 0.1 per cent do no harm and may do some good when used in addition to adequate hydration of the patient and his inspired air.

Although trypsin is capable of liquefying bronchial secretions when administered as an aerosol, the incidence of serious reactions has been too great to warrant recommendation that preparations of this enzyme available at present be used on a wide scale. Trypsin may be advantageously used by local application. Pancreatic dornase has proved less toxic than trypsin and may find usefulness in the liquefaction of purulent secretions. Such patients as children with cystic fibrosis, severe asthmatics with diffuse mucoid plugging, particularly when the mucoid plugs consist largely of leukocytes (eosinophils or polymorphonuclear leukocytes), and patients

with chronic suppurative bronchitis or bronchiectasis benefit most from the use of pancreatic dornase when administered properly. The greatest benefit can be achieved from the use of such an agent when it is administered after the previous application of bronchodilator and wetting agents and superheated aerosols to open and clear the bronchial tree of all secretions that are movable prior to the administration of the enzyme, and by careful attention to proper breathing techniques. In some instances, particularly in patients with diminished pulmonary reserve and thus an ineffective cough, rapid mobilization of secretions may precipitate an apparent worsening of airway obstruction necessitating provision for more adequate drainage.

The use of antimicrobial drugs by inhalation has produced a larger number of susceptibility reactions without a demonstrable superiority to other routes of administration in patients with bronchopulmonary disease. On theoretic grounds, it seems reasonable to expect that tissue which is not devitalized, and therefore maintains some blood supply, can with adequate dose schedules achieve as high a concentration of drug by orally or systemically administered antimicrobials as by the inhalation route. In exceptional circumstances, polymixin, neomycin, or bacitracin may be given by aerosol when specific culture and susceptibility studies indicate their use in patients, such as small children, in whom the drug might not otherwise be given because of untoward systemic effects. In these situations, many times the ordinary parenteral dose can be given by the aerosol route owing to the fact that these agents are not readily absorbed across the respiratory membrane.

Humidification of dry air is indicated in the presence of gross drying of the upper airways, respiration by tracheostomy, and the presence of thick tracheobronchial exudate or decreased ability to clear exudate and secretions through the trachea. Whereas the use of medication may be important in the prevention of airway drying and the mobilization of secretions, its effects should not be confused with those of humidification. Heated aerosols provide the best means of humidification and are classified as a *tepid aerosol* when delivered at or near body temperature and *superheated aerosol* when inspired at temperatures in excess of body temperature (not to exceed 125°F.) The usual *side stream* nebulization technique commonly used in continuous assistance of breathing by means of intermittent positive pressure does not provide adequate humidification. This can best be accomplished by means of mist generators such as *mainstream* nebulizers so equipped as to permit the passage of a stream of gas from the respiratory pump directly through the nebulizer and over the jets so that maximal humidification occurs. The decision to use tepid aerosol or superheated aerosol depends on the volume deposition of solution desired. Thus the temperature and character of the solution are altered to meet the demands of the problem. Higher temperatures and more concentrated solutions result in greater deposition of aerosol and more effective "wetting" of the bronchial tree.

Thomas B. Barnett
Benjamin Burrows
Edward Dunner
John R. Durrance
Attilio D. Renzetti, Jr.
Herbert Schmidt
William W. Stead
Donald L. Paulson, *Chairman*

The Use of Dihydrostreptomycin in Tuberculosis

A Statement of the Committee on Therapy

It is well established that dihydrostreptomycin is more toxic to the auditory system than is streptomycin, while the latter is more prone to produce vestibular damage. The vestibular damage produced by streptomycin occurs after relatively large doses of that drug; it does not progress after cessation of therapy, and may be compensated for to a considerable degree. In contrast, deafness may occur following small doses of dihydrostreptomycin and may progress or even begin after the antimicrobial has been discontinued. Once noted, hearing loss is usually irreversible and may be characterized by a selective loss of speech discrimination which is difficult to treat. Although the phenomenon is apparently rare (as indicated by the widespread use of dihydrostreptomycin in the therapy of tuberculosis without significant ototoxicity), the unpredictability of dihydrostreptomycin in producing hearing loss, the difficulty in recognition of early toxic effects, and the irreversibility of the damage produced indicate that dihydrostreptomycin should not be used in the routine treatment of common bacillary infections, nor should this drug be used in commercially available combinations with other antimicrobials.

Since streptomycin alone, when employed in the usual antituberculosis dosage (no more than 1 gm. daily), has not been associated with a high degree of vestibular damage, and, since there is no definite proof of the superiority of regimens which include dihydrostreptomycin, the use of mixtures of streptomycin and dihydrostreptomycin or dihydrostreptomycin alone is not recommended for the routine therapy of tuberculosis. At present, the use of dihydrostreptomycin in tuberculosis should be limited to special cases in which there is a particular reason to avoid the vestibular toxicity of the latter drug, and in the rare instance of specific hypersensitivity to streptomycin. The risk of significant deafness from dihydrostreptomycin should not preclude its use in those circumstances in which the indications are compelling; for these special instances the continuing availability of dihydrostreptomycin is desirable.

THOMAS B. BARNETT
BENJAMIN BURROWS
EDWARD DUNNER
JOHN R. DURRANCE
ATTILIO D. RENZETTI, JR.
HERBERT W. SCHMIDT
WILLIAM W. STEAD
DONALD L. PAULSON, *Chairman*

The Chemotherapeutic Management of Treatment Failures and Relapses in Pulmonary Tuberculosis

A Statement of the Committee on Therapy

Introductory remarks: In a disease as variable and unpredictable as tuberculosis, it is not surprising that, despite the number of antituberculosis agents available, treatment failures and relapses still occur. The management of previously untreated patients consists of giving isoniazid in adequate doses, usually combined with streptomycin or para-aminosalicylic acid (PAS) or both. This has become fairly well standardized. The effective treatment of failures and relapses, on the other hand, continues to present a therapeutic enigma. The multiplicity of available drugs requires an organized plan of treatment to attain the best results. This statement is offered in an effort to consolidate current opinions and practices in the hope that it might lead to the formulation of a better over-all plan of management at the outset of re-treatment. It must be recognized, however, that the application of any recommended regimen may have to be modified because of factors related to the individual patient, i.e., hypersensitivity, liver and renal impairment, et cetera.

Definitions: The term *treatment failure* includes those patients in whom the total therapeutic program (drugs, time, and surgery when appropriate) has been unable to bring about an inactive state (NTA Standards). *Relapse* is defined as reactivation of the disease after a period of inactivity. In either instance, the bacilli may or may not be resistant to the chemotherapeutic agents previously employed.

Treatment failures: To avoid a haphazard expenditure of all available antituberculosis agents, the patient's total problem should be carefully evaluated early, including the possible need for surgical intervention. Assuming that diagnostic errors have not been made, i.e., carcinoma, infections with unclassified mycobacteria, fungi, et cetera, and that the patient has taken the medication in adequate dosage, the following recommendations are made pertaining to the selection of drugs for treatment failures:

1. For the patients who return for therapy after a previously inadequate period of therapy, the same drugs should be used in standard dosage pending susceptibility studies if rapid progression of the disease is not taking place. For these patients, the addition of a third drug prior to obtaining evidence based on susceptibility studies is not recommended.

2. If rapid progression of the disease is taking place, a change in drug therapy is recommended by substitution or addition of one or more new drugs.

3. A combination of two or more of the following drugs: cycloserine, pyrazinamide, viomycin, or kanamycin may be used. Their short-term effectiveness should be taken into consideration in formulating a treatment program. (Reported results of clinical trials with thioamide, although encouraging, are too preliminary to include in a recommendation at this time.)

4. Streptomycin or PAS should be discontinued whenever information from susceptibility studies indicates complete resistance, since this signifies loss of drug efficacy. The same, however, may not be true for isoniazid, and its use may be continued.

5. Patients classified as treatment failures who are candidates for thoracic surgery may benefit from a course of therapy of short duration consisting of pyrazinamide with cycloserine or viomycin if these drugs have not been given previously.

6. Patients not previously treated with isoniazid should be given isoniazid as the first drug of choice in any drug combination to be used.

7. The tetracyclines may be used as a replacement for PAS in case of resistance of the organisms or severe intolerance. Results with thiocarbanidin or streptovaricin have not justified their substitution for PAS.

8. When effective drug coverage is lacking, patient activity should be limited in contrast to the freedom of ambulation permitted original treatment cases with effective drug coverage and good prognosis.

9. Proof is lacking that the addition of adrenocorticosteroids and corticotropin in the treatment of selected hospitalized patients accomplishes a better end result than can be obtained with chemotherapy alone. Adrenocorticosteroids and corticotropin should not be employed for such patients unless there is satisfactory evidence of susceptibility of the organisms to the drug being administered.

Relapses: The incidence of relapse has been reduced considerably, due to the advent of long-term chemotherapy and especially since the introduction of isoniazid therapy in 1952. The combination of drugs chosen in the management of relapses depends on the demonstrated susceptibility of the patient's organisms. Relapse in spite of apparently adequate drug therapy may be

regarded as evidence of the emergence of resistance to one or more of the agents that had been used in previous treatment. The recommendations pertaining to treatment failures apply equally to relapses.

Dosage:

(a) Streptomycin: 0.5–1 gm. daily or 1 gm. two or three times a week, intramuscularly.

(b) Isoniazid: 3–5 mg. per kg. of body weight per day orally. Higher doses of 12 to 24 mg. per kg. may increase therapeutic efficacy, particularly in patients in whom rapid inactivation of isoniazid is suspected. Its use in such higher dosages should be accompanied by a minimum of 50 mg. of pyridoxine per day to reduce the risk of isoniazid neurotoxicity.

(c) PAS: Sodium PAS is the generally preferred form of PAS although its other salts also are effective (15 gm. of the salt or 12 gm. of the acid daily). When sodium restriction is important, one of the other salts of PAS should be used.

(d) Cycloserine: 0.5 gm. daily in divided doses orally. Dosages above 0.5 gm. per day may occasionally be warranted but entail risk of neurotoxicity which may be modified by the employment of pyridoxine.

(e) Pyrazinamide: 20 to 40 mg. per kg. per day orally, in divided doses. Hepatotoxicity constitutes a complication of higher dosage in prolonged therapy.

(f) Viomycin: 1 to 2 gm. twice weekly, intramuscularly. Viomycin should be used with caution in patients with pre-existing renal disease.

(g) Tetracyclines: 2 to 4 gm. orally daily in divided dosages.

(h) Kanamycin: With 1 gm. intramuscularly daily in divided dosages its use may lead to deafness in a short period of time, which limits its therapeutic value in any long-term program of treatment. The reported delay or prevention of eighth-nerve toxicity by reduction of dosage to less than 4 gm. weekly needs to be confirmed. Kanamycin, at the present time, appears to be of more value in nontuberculous infections.

(i) Thioamide: 0.5 to 1.0 gm. daily orally, in divided doses.

Duration of chemotherapy: At least eighteen months of uninterrupted chemotherapy and often a much longer period is required to achieve maximal benefits. The optimal duration of treatment is still not known. Hospitalization for treatment failures and relapses is very important. The short-term effectiveness (three to six months) of drugs which will be available for these cases makes the surgical intervention at the earliest possible time important in the consideration of any plan of treatment.

THOMAS B. BARNETT
BENJAMIN BURROWS
EDWARD DUNNER
JOHN R. DURRANCE
ATTILIO D. RENZETTI, JR.
HERBERT SCHMIDT
WILLIAM W. STEAD
DONALD L. PAULSON, *Chairman*

The Use of Corticosteroids in the Treatment of Sarcoidosis

A Statement of the Committee on Therapy

For many years the medical profession has been trying to find the cause, as well as a satisfactory method of treatment, of sarcoidosis. The cause remains unknown, and the only drugs that have in any way influenced the course of the disease are the corticosteroids. The hazards of using these drugs are well known, and consequently one must have definite indications for using them. Probably not more than 10 per cent of patients with this disease require corticosteroids. The indications for their use in this disease are not entirely clear, and therapy must be based on individual evaluation.

Indications for the Use of Corticosteroids

1. Involvement of a vital organ such as the brain, spinal cord, or heart is an indication for the initiation of treatment as early as possible.

2. Acute or subacute involvement of the eye requires early treatment to prevent or limit progressive damage to the eye and possible blindness.

3. Progressive pulmonary parenchymal involvement as manifested by increasing symptoms, unfavorable changes in roentgenograms of the chest, or deterioration of pulmonary function, may indicate vigorous use of steroid therapy.

4. Patients who have persistent hypercalcemia should receive treatment early. Corticosteroids will usually reduce serum calcium to normal and prevent or limit renal complications.

5. Patients who are acutely or subacutely ill, as evidenced by loss of weight, fever, arthralgia, liver dysfunction, or symptomatic splenomegaly.

6. Patients who have progressive and disfiguring lesions of the skin. Patients with sarcoidosis who, according to our present knowledge of the disease, should not be treated with corticosteroids are:

(a). Patients who have only bilateral hilar or paratracheal lymphadenopathy with minimal or no symptoms. In such patients the disease usually follows a favorable course, whether the patients are treated with corticosteroids or not.

(b). Patients who have nonprogressive, pulmonary parenchymal lesions with no symptoms or minimal symptoms.

(c). Patients who have chronic fibrotic pulmonary parenchymal lesions that are known to have been stable for long periods.

Method of Treatment with Corticosteroids

Corticosteroid therapy can be given by mouth or locally for ocular or dermal lesions. Some of the drugs that have been used orally or systemically are cortisone, hydrocortisone, prednisone, prednisolone, corticotropin and, more recently, triamcinolone and dexamethasone. After initially favorable response, the dosage should be reduced to the minimum consistent with maintenance of the effect. Local treatment has been used, including various steroid ointments, intradermally administered solutions of hydrocortisone with and without hyaluronidase, solutions of hydrocortisone administered subconjunctivally, and cortisone and hydrocortisone in eye drops.

The concomitant use of antituberculosis drugs is indicated in all patients whose sarcoidosis is being treated with steroids and who react positively to the tuberculin test.

Duration of Treatment

The optimal duration of treatment is difficult to predict in any patient. When the original involvement of an organ has been severe, corticosteroids may profitably be used for a year or longer. In considering prolonged corticosteroid therapy in sarcoidosis, one should keep in mind the risk of undesirable side effects and the frequent difficulties in discontinuance.

THOMAS B. BARNETT
BENJAMIN BURROWS
EDWARD DUNNER
JOHN R. DURRANCE
ATTILIO D. RENZETTI, JR.
HERBERT W. SCHMIDT
WILLIAM W. STEAD
DONALD L. PAULSON, *Chairman*

NOTICES

The following dates and locations of the next four annual meetings of the National Tuberculosis Association and the American Thoracic Society have been selected and approved:

1961—Cincinnati, Ohio—May 21–26
1962—Miami Beach, Florida—May 20–25
1963—Denver, Colorado—May 12–17
1964—New York, New York—May 24–29

POSTGRADUATE COURSE IN ALLERGY

A continuous course of two weeks' duration is being offered by the departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center from 9:00 A.M. to 5:00 P.M. from February 27 to March 10, 1961. The tuition fee is $175.00. Enrollment is limited. Dr. Louis Tuft is course director, with Drs. George Blumstein and Merle M. Miller as associate directors.

An outstanding faculty has been assembled to review the basic principles of immunology and allergy as applied to clinical practice. Emphasis will be given to the methods of diagnosis and management of the allergic patient. The course is designed for physicians desirous of extending their knowledge of allergy. It could serve as an introductory course for those about to enter the field or as a review course for practicing allergists.

For brochure and application forms write to: Dr. George Blumstein, % Temple Medical Center, Philadelphia 40, Pennsylvania.

AMERICAN COLLEGE OF CHEST PHYSICIANS: INTERIM SESSION
Washington, D.C., November 26–28, 1960

The American College of Chest Physicians will hold its annual Interim Session at the Shoreham Hotel in Washington, D.C., this November. The scientific sessions will be held on Saturday and Sunday, November 26 and 27. Monday, November 28, will be reserved for administrative sessions. Dr. M. Jay Flipse, Miami, Florida, President of the College, will preside.

Dr. Joseph W. Peabody, Jr., Washington, D.C., and his committee, have arranged a scientific program of exceptional interest including Symposia on Congenital Bronchopulmonary Disorders, The Role of Steroid Therapy in Chest Diseases, and Current Therapeutic Issues.

A highlight of the program will be the Fireside Conferences on Sunday evening, November 27. In addition, there will be three round-table luncheon discussions on both Saturday and Sunday. These will feature prominent speakers discussing various aspects of heart and lung diseases.

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

ABSTRACTS

Edited by EDWIN D. KILBOURNE
Editorial Assistant: TERRI MANN

VOLUME 82 November 1960 ABST. NO. 5

The Editor recognizes the inevitable incompleteness and arbitrary selectivity of any abstracting service, including this one. It is his belief that the usefulness of the present Abstracts section will be enhanced if the reader is informed of the general purpose of the abstracts and the criteria employed in their selection.

It is the purpose of the Abstracts section to acquaint the diversified and international readership of the REVIEW with the gist of original and scientific articles which are related to the general subjects of tuberculosis or respiratory diseases implicit in the title of the journal. In this connection, 42 abstracters systematically review 239 journals which represent 36 countries and which are published in 22 languages. In most instances, abstracters cover journals in fields of their special competence. It is evident that the diverse interests of the readers of the REVIEW dictate a balanced selection of clinical, laboratory, and epidemiologic studies. Such selection will often preclude the publication of articles equal in scientific merit to many presented here.

In the publication of abstracts, cognizance is taken of the extent to which the journals yielding them are circulated. Articles from journals of wide circulation may be mentioned by title only. This space-saving device is also employed for articles which defy condensation without the omission of essential data or discussion. The attention of readers is thus directed to the existence of papers which are no less important because they are not summarized.

(Requests for further information on abstracted articles should be directed to the author of the article at the address indicated by an asterisk (*) in each abstract title.)

ABSTRACTERS

HANS ABELES, M.D., New York, N. Y.
ITALO ARCHETTI, M.D., Rome, Italy
A. L. LOOMIS BELL, JR., M.D., N. Y., N. Y.
ABRAHAM BORNSTEIN, M.D., Brooklyn, N. Y.
JOSÉ FERNANDO CARNEIRO, M.D., Porto Alegre, Brazil
ERIC J. CASSELL, M.D., New York, N. Y.
A. G. COHEN, M.D., New York, N. Y.
ÉDWARD DUNNER, M.D., Silver Spring, Md.
G. FEDDERS, M.D., Anoka, Minn.
R. MUNRO FORD, M.D., Adelaide, South Australia
HILDA GARCIA DE LA NOCEDA, M.D., Rio Piedras, Puerto Rico
JAAKKO HAAPANEN, M.D., Tampere, Finland
H. J. HENDERSON, Philadelphia, Pa.
LEROY HYDE, M.D., Long Beach, Calif.
JAN ILAVSKY, M.D., Pompton Plains, N. J.
WILLIAM M. M. KIRBY, M.D., Seattle, Wash.
MIROSLAW KOMARJANSKI, M.D., Brecksville, O.
NICHOLAS C. LAIOS, M.D., New York, N. Y.
EVA SOTO-LEAKE, Charlottesville, Va.
GEORGE C. LEINER, M.D., New York, N. Y.
VERA LEITES, M.D., New York, N. Y.
JOHN LORBER, M.D., Sheffield, England
ERNA LYON, M.D., Jamaica, N. Y.
RODGER E. MACQUIGG, M.D., Albuquerque, N. M.
IVAN V. MAGAL, M.D., Charlottesville, Va.
THEODORE H. NOEHREN, M.D., Buffalo, N. Y.
F. PEREZ PINA, M.D., Waltham, Mass.
CYNTHIA H. PIERCE, PH.D., New York, N. Y.
ANNA V. POPOFF, M.D., Castle Point, N. Y.
EDGAR A. RILEY, M.D., New York, N. Y.
BERNARD ROGOFF, M.D., New York, N. Y.
CHARLES M. ROSS, M.D., Buffalo, N. Y.
ELLIOT A. ROUFF, M.D., Los Angeles, Calif.
JEROME SCHULMAN, M.D., New York, N. Y.
ELMER J. SHABART, M.D., Livermore, Calif.
HAROLD J. SIMON, M.D., Palo Alto, Calif.
MAURICE J. SMALL, M.D., Staten Island, N. Y.
WILBUR J. STEININGER, M.D., Northville, Mich.
ISAO TATENO, M.D., Tokyo, Japan
ZOLTAN VIRÁGH, M.D., Outwood, Ky.
WILLIAM A. ZAVOD, M.D., Mount Vernon, N. Y.

NONTUBERCULOUS THORACO-PULMONARY DISEASE

Pulmonary Abscess in Infancy and Childhood: Report of 18 Cases. T. C. MOORE* and J. S. BATTERSBY. *Ann Surg*, April, 1960, 151: 496–500. (*Indiana U. Med. Center, Indianapolis)

A 25-year experience is reported with 18 cases of pulmonary abscess in infancy and childhood. The pathogenesis of the abscess was regarded as post-pneumonic in the majority of cases. Fever was the most common symptom: it was encountered in 15 of the 18 cases. It was followed, in order of frequency, by cough, purulent sputum, weight loss, and hemoptysis. The right lung was involved in abscess formation approximately twice as often as the left. There appeared to be a greater tendency toward right middle lobe involvement in the pediatric age group. The relative incidence of hemolytic *Staphylococcus aureus* infection was greater in the pediatric age group. Eleven of the patients were managed by "nonoperative" measures, and only 2 recovered. Nearly ½ of the deaths resulted from brain abscesses or purulent meningitis. All 7 of the patients recovered on whom a direct surgical attack on the abscess was carried out. The incidence of pulmonary abscess has decreased markedly in recent years in both adult and pediatric age groups due largely to the availability and skillful use of a variety of antimicrobials in acute pulmonary infections. The major difficulty at the present time arises in those cases in which the infection is due to an organism which is resistant to the available antibacterial agents. It is in this group of cases that pulmonary resection is of value.—M. J. SMALL

Isolated Multiple Nodular Pulmonary Amyloidosis. L. WEISS*. *Amer J Clin Path*, April, 1960, 33: 318–329. (*Cedars of Lebanon Hosp., Los Angeles, Calif.)

The clinical and pathologic findings in a patient with isolated nodular pulmonary amyloidosis are presented and the pathogenesis is discussed. —E. DUNNER

Bacteriophage Typing of Staphylococci from Asthmatic Patients. S. J. PRIGAL*. *JAMA*, March 26, 1960, 172: 1361–1367. (*New York Med. College, N. Y., N. Y.)

Hemolytic staphylococci are frequently encountered in patients with recurrent or chronic sinorespiratory infections, with or without associated asthma. Bacteriophage typing of these coagulase-positive staphylococci indicates that some families with sinorespiratory problems become colonized with staphylococci. Persons in these families are more apt to have asthma. No one type of Staphylococcus can be etiologically related to infectious asthma.—H. ABELES

Slowly Progressing Bronchial Cancer (in French). M. CHAUVET*. *Schweiz Med Wschr*, March 12, 1960, 90: 270–274. (*Clinique Universitaire, Geneva, Switzerland)

Eight cases of bronchial carcinoma are presented, with a clinical follow-up of more than 2 years. In 6 patients a squamous-cell carcinoma was found, but in 2 instances the tumor was of the undifferentiated "oat-cell" type, 1 in a patient with a survival time of more than 14 years. In 3 patients no metastases could be demonstrated at autopsy, while in another case dissemination was limited to the pulmonary lymph nodes. Thus, the length of time from the first manifestations of the disease should not be considered a major determinant in the choice of therapy.
—J. HAAPANEN

Clinical Features of Lung Cysts (in German). J. HOFERICHTER*. *Deutsch Med Wschr*, February 12, 1960, 85: 258–261. (*Chirurgische Universitätsklinik, Erlangen, Germany)

In a series of 20 congenital lung cysts, either pulmonary resection or cystectomy was performed in 15. The indication for operation was usually infection of the cyst and/or surrounding tissue: in 3 cases, hemoptysis; and in 3 the operation was started as an exploratory thoracotomy. In the presence of an infection, the exact diagnosis of a congenital cyst is possible only after eliminating focal and perifocal inflammatory signs by means of postural drainage and antimicrobial treatment. Only then will roentgenographic, bronchographic, and bronchoscopic examinations reveal the nature of the disease, which is often misdiagnosed as tuberculosis (7 of 20 cases in this series).—J. HAAPANEN

Pulmonary Cytology (Editorial). L. B. WOOLNER*. *Amer J Clin Path*, April, 1960, 33: 339–340. (*Mayo Clinic, Rochester, Minnesota)

Serologic Evidence of Infection with Eaton Agent in Lower Respiratory Illness in Childhood. R. M. CHANOCK*, M. K. COOK, H. H. FOX, R. H. PARROTT, and R. J. HUEBNER. *New Engl J Med*, March 31, 1960, 262: 648–654. (*National Institute of Allergy and Infectious Diseases, Bethesda, Md.)

The role of Eaton agent (previously associated with cold-agglutinin-positive pneumonia in adults) in lower respiratory tract disease in infants and children was sought in a controlled study em-

ploying the indirect fluorescent-antibody technique. A group of 152 infants and children with lower respiratory tract illness and 64 infants and children without respiratory disease were investigated. The fluorescent-antibody findings suggested that infection with Eaton agent or an antigenically related agent was associated with approximately 10 per cent of lower respiratory tract illness over a period of 16 months in the Washington, D. C., area. Evidence is presented that such an infection was associated with the respiratory illnesses studied, and was not acquired during the period of hospitalization. Eaton agent appeared to infect in an endemic fashion. Evidence of infection was detected during 10 of the 16 months of the study period, and during all seasons of the year (after authors' summary).
—M. J. SMALL

Bronchiolar Ectasia. A Report of Twelve Cases. H. STURTEVANT* and H. KNUDSON. *Amer J Roentgenol*, February, 1960, 83: 279–282. (*U. S. Air Force Hosp., Lackland Air Force Base, Texas)

A review of 523 bronchograms taken during 3 years at the above-named hospital disclosed 12 well-defined cases of bronchiolar ectasia. The diagnoses were made solely on the basis of the roentgenographic appearances. A correlation of the clinical findings and symptomatology was then attempted. All of the patients had symptoms compatible with chronic bronchitis or bronchiectasis except 1, who had a persistent pneumonitis in the posterior segment of the right upper lobe. This patient was cleared of all possibility of tuberculosis. Of particular interest was 1 case showing multiple ectatic changes of the bronchioles in April, 1958, following a staphylococcal pneumonia but, 1 year later, repeat bronchography failed to show definite evidence of the process, suggesting that this entity may be a reversible process.—T. H. NOEHREN

The Incidence of Peptic Ulceration in Chronic Obstructive Pulmonary Emphysema. L. ZASLY*, G. BAUM, and J. RUMBALL. *Dis Chest*, April, 1960, 37: 400–405. (*V. A. Hosp., Coral Gables, Florida)

A statistical study of hospitalized patients indicated a significantly increased incidence of chronic peptic ulcer in chronic obstructive pulmonary emphysema. Twenty-two per cent of those studied had evidence of both conditions, while a control group in the same age bracket without emphysema revealed an incidence of 2.7 per cent.—E. A. ROUFF

Acute Esophagitis in Pneumonia (in German). A. OTT*. *Wien Klin Wschr*, April 11, 1960, 72: 227–229. (*Vienna, Austria)

Dysphagia may occur in the presence of pulmonary disease due to: (*1*) direct traction of mediastinal pleural adhesions, (*2*) traction caused by shrinkage of a lobe by way of its main bronchus on the trachea, heart, and esophagus, and (*3*) pressure differences in the thorax. Four cases of pneumonia accompanied by dysphagia are reported. Roentgenographic examinations revealed the presence of acute localized esophagitis. In these cases there was swelling of the hilar lymph nodes. It is believed that the inflammatory process of these lymph nodes resulted in periesophagitis and esophagitis.—G. C. LEINER

Farmer's Lung: Report of Two Cases. W. P. BALDUS* and J. B. PETER. *New Engl J Med*, April 7, 1960, 262: 700–705. (*U. of Minnesota Hospitals, Minneapolis)

Farmer's lung is recognized as a clinical entity in which the development of respiratory symptomatology follows the inhalation of dust from moldy hay, silage, or grain. The 2 cases reported are of special interest because lung biopsies were obtained; symptoms were reproduced in 1 patient by deliberate exposure to dust during the period of study, and the 2 patients depict the variable course of this condition. Dyspnea is the chief symptom in almost all cases and may be accompanied by fever, chills, nonproductive cough, malaise, and weight loss. The acute, isolated attack is manifested by the rapid onset of symptoms that subside after a few days. The subacute phase is characterized by progressive dyspnea and cough resulting from repeated exposure to mold dust over a period of a few months. Pulmonary rales are present, and the typical roentgenographic picture is seen. If, at this stage, the patient is removed from the dusty environment, the symptoms and roentgenographic abnormalities usually clear in 1 to 3 months. This subacute phase is typified by Case 1. The chronic phase occurs after repeated exposure over a period of years. The patient is left quite severely incapacitated with irreversible changes of emphysema and pulmonary fibrosis. Case 2 represents this type.

The pulmonary roentgenographic changes in farmer's lung are nonspecific. Fine nodular densities are seen scattered diffusely throughout both lung fields, but are more prominent in the central portions. The pathologic changes in the lungs in the present cases are similar to those described by others, namely, focal noncaseating granulomas surrounded by giant cells and accompanied by an interstitial infiltration of histiocytes and lymphocytes. The etiology of farmer's lung remains

obscure, but all authors agree that it is directly related to the inhalation of mold dust. It seems likely that a fungus is essential in the causation of this disease; however, its exact role has not yet been determined. The reaction of Case 1 to the inhalation of the dust of moldy hay while under observation in the hospital lends support to the hypothesis of a hypersensitivity reaction. —M. J. SMALL

Pulmonary and Allergic Manifestations of Cystic Fibrosis of the Pancreas. A. M. FISHER*, T. E. VANMETRE, JR., and W. L. WINKENWERDER. *Amer J Med Sci*, April, 1960, 239: 430–438. (*Johns Hopkins Hosp., Baltimore, Maryland)

The progress of the condition in 2 young adults with cystic fibrosis of the pancreas illustrates the fact that the manifestations of the disease may vary greatly. Consideration of a fairly large series of patients indicates that a relatively high proportion develops allergic manifestations of the atopic type, the reason for which is not clear, but which may be related to the basic pathophysiology of the underlying disease. The prognosis is poor on the whole and determined for the most part by the severity of the pulmonary complications, which may be aggravated by the development of atopic respiratory disturbances. Therapeutic measures include bronchodilators, pancreatic enzymes, fat-soluble vitamins, corticosteroids, and antimicrobials at the time of acute infections. If allergic rhinitis and asthma of the atopic type occur, desensitization and avoidance of significant antigens are helpful.—W. J. STEININGER

Prednisolone Maintenance Therapy in Chronic Pulmonary Heart Disease. J. N. MICKERSON*. *Brit Heart J*, April, 1960, 22: 220–226. (*Charing Cross Hosp., London, England)

The author considers that the long-term outlook of chronic asthmatic patients may be so bad, because they so often develop pulmonary heart failure, that long-term prednisolone treatment is justifiable in spite of its apparent disadvantages. Prednisolone was administered to 4 such patients, 3 of whom already had chronic pulmonary heart disease. The duration of treatment was 9–18 months. Coexistent heart failure was relieved and all were maintained free from symptoms and unrestricted in their activities. The pulmonary P-wave on electrocardiographic tracings (which in itself is considered an indication for long-term prednisolone therapy), reverted to normal and reflected improvement in the pulmonary hemodynamics during steroid therapy.—J. LORBER

Nodular Muscular Hyperplasia in the Lungs of South African Miners. C. CHATGIDAKIS* and H. RAND. *AMA Arch Industr Health*, February, 1960, 21: 160–164. (*South African Council for Scientific Research, Johannesburg)

Smooth muscle, in the normal lung, is confined to the walls of the blood and lymphatic vessels, the bronchi, bronchioles, and alveolar ducts. There is no smooth muscle in the pleura or interstitial tissue of human lungs under normal conditions. The appearance of smooth muscle in these areas of the lung is a pathologic entity, and has been termed "muscular hyperplasia," "muscular cirrhosis of the lungs," or "pulmonary myomatosis." The presence of an unduly high incidence of nodular muscular hyperplasia in the lungs of South African miners is reported. The significance of this phenomenon is not clear, but an etiologic relationship to dust exposure is suggested. The origin of the smooth muscle has not been determined with certainty, but the features suggest a close relationship to lymphatic vessels. Nodular muscular hyperplasia may be confused with true silicosis roentgenographically and at post-mortem examination. No increase in muscle of the bronchi, bronchioles, and blood vessels is found in these cases.—T. H. NOEHREN

Congenital Anomalies of the Lung. J. WIER*. *Ann Intern Med*, February, 1960, 52: 330–348. (*Fitzsimons Army Hosp., Denver, Colorado)

Congenital anomalies of the lung in the adult are being recognized with increasing frequency, and an awareness of the possibility of their presence in the differential diagnosis of pulmonary disease may lead to the correct diagnosis during the course of an adequate clinical examination, including roentgenogram of the chest. A brief review of the congenital anomalies of the lung is presented, emphasizing those occurring in the adult. Many of these anomalies may be suspected or diagnosed during the course of a careful examination, including a roentgenogram of the chest. Although anomalies of clinical importance are not frequent in occurrence, failure to consider them in differential diagnosis may lead to embarrassing errors in diagnosis and management. —T. H. NOEHREN

Pulmonary Aspergillosis Associated with Radiation Pneumonitis. D. BRUCE NEILSON*. *Scot Med J*, December, 1959, 4: 557–562. (*Victoria Infirmary, Glasgow, Scotland)

Although primary pulmonary infection by the fungus Aspergillus is rare, it is not uncommon as a secondary infection in bronchiectasis, carcinoma of the bronchus, bronchogenic cyst, and pulmo-

nary abscess. There is a definite occupational hazard among agricultural workers, fur cleaners, and wig makers. The case is described of a woman of 57 years who had a large thin-walled cyst in the right lung. She developed a scirrhous carcinoma of the breast which was treated by irradiation (total dose 6,200 r.). Eighteen months later she developed a respiratory tract infection with copious mucopurulent sputum. She now had a fluid level in the cyst. The right lower lobe which contained the cyst was removed, and from the wall of the cyst *Aspergillus fumigatus* was grown. Meanwhile, a variety of antimicrobial treatment caused dissemination of the Aspergillus infection in the lungs, which was only arrested after the nature of the infection was recognized and treated first with nystatin and later with oleandomycin. It is suggested that the pneumonitis produced by radiation devitalized the lung and so allowed the growth of inhaled spores of Aspergillus.
—J. LORBER

Transmission of North American Blastomycosis. Possible Case of Transmission from Dog to Human. R. M. SCHWARTZMAN*, R. M. FUSARO, and M. ORKIN. *JAMA*, December 19, 1959, 171: 2185–2189. (*U. of Pennsylvania, Philadelphia)

A 52-year-old man died of disseminated North American blastomycosis. Three months earlier a dog had died of the same disease in the same community where, ordinarily, blastomycosis is a rare disease. It is possible that a transmission of blastomycosis occurred from dog to human.
—H. ABELES

Chronic Active Pulmonary Histoplasmosis with Cavitation. D. LOEWEN*, J. PROCKNOW, and C. LOOSLI. *Amer J Med*, February, 1960, 28: 252–280. (*Macon County TB Sanatorium, Decatur, Illinois)

The clinical and laboratory characteristics of 13 patients with chronic active pulmonary histoplasmosis are described. They were all initially considered to have tuberculosis and, indeed, the roentgenographic findings and clinical manifestations are indistinguishable from tuberculosis. Treatment in selected cases, as in tuberculosis, can be successfully carried out by surgical resection of the lesions. With the exception of amphotericin B, drug therapy has not been proved effective in patients with bilateral cavitation.

In highly endemic areas, physicians and health workers should be alerted to the fact that many cases of histoplasmosis may be found in tuberculosis sanatoriums (after authors' summary).
—T. H. NOEHREN

Mucormycosis. O. GABRIELE*. *Amer J Roentgenol*, February, 1960, 83: 227–235. (*Grace–New Haven Community Hosp., New Haven, Conn.)

Four cases of mucormycosis, all fatal, are reported in patients aged 6½, 39, 50, and 72 years. Mucormycosis is a rapidly fatal disease characterized by acute inflammation and vascular thrombosis, caused by invasion of the walls and lumina of blood vessels by the fungus. The reported cases have almost invariably been associated with some underlying disease, usually diabetes mellitus, but including leukemia under treatment, nephritis, and cirrhosis. Pulmonary involvement is manifest as a lobular pneumonia with abscess formation and lack of response to therapy. Infarctions are not recognized as such. Although the roentgenographic changes are not characteristic, awareness of the entity and its association with predisposing metabolic disturbances may make it possible to consider the diagnosis while the disease is still in its controllable stage. No specific treatment is known. Treatment consists primarily of management of the underlying disease, usually diabetes mellitus. Drugs such as antileukemic agents, cortisone, et cetera, should not be used as there is evidence to indicate that these facilitate initiation and spread of the fungous infection.—T. H. NOEHREN

Pulmonary Mycosis in Brazil (in Portuguese). J. F. CARNEIRO*. *Rev Bras Med*, March, 1960, 17: 216–231. (*Faculdade de Medicina, Porto Alegre, Brasil)

South American blastomycosis is the pulmonary mycosis most frequently seen in Brazil. Cases of North American blastomycosis and coccidioidomycosis have not so far been seen in Brazil. Pulmonary histoplasmosis has been observed several times; one small epidemic of this disease is known to have occurred. A case is presented of a young girl with cervical, mediastinal, and abdominal lymph node calcification resulting from generalized severe tuberculosis in early childhood. This patient stopped reacting to tuberculin, but became a reactor to histoplasmin later on. A word of caution is given against a diagnosis of histoplasmosis, present or past, based only on the existence of a positive reaction to histoplasmin and a negative reaction to tuberculin. The antimicrobial action of *Aspergillus fumigatus* against the tubercle bacillus is stressed. A case of pulmonary moniliasis showing high pulmonary uptake of I^{131} is presented (after author's summary).
—J. F. CARNEIRO

Clinical Observations and Therapeutic Experiences in Sarcoidosis (in German). K.-B. LEE*. *Beitr Klin Tuberk*, September, 1959, 120: 388–

407. (*Taegu, Korea)

The medical history and symptomatology, as well as the hematologic, roentgenographic, immunologic, and histologic findings in 41 patients with sarcoidosis are analyzed. All but 2 were treated with antituberculous drugs, 16 of them only with Tebafen (a preparation of isoniazid and thiosemicarbazone). The controls were 27 patients who were not given antimicrobial treatment. In support of the theory of a lymphatic diathesis in sarcoidosis, it is noted there were 10 patients who underwent an appendectomy, and 13 had their tonsils removed. All of the patients treated with Tebafen improved considerably, while those on the other antituberculous regimen were not different from the untreated cases, in which only spontaneous remissions occurred. The corticosteroids showed only little or no beneficial effect on the course of the disease. In 5 patients, sarcoidosis developed following BCG vaccination. —Z. VIRÁGH

Costal Osteomyelitis Erroneously Treated as Tuberculous Pyothorax. Report of a Case (in Japanese). K. SAITO*, M. MATSUDA, and T. IWAZAKI. *Jap J Thor Surg*, April, 1960, 13: 321–323. (*National Tochigi Hosp., Utsunomiya, Japan)

Osteomyelitis of the rib is a rare condition and does not amount to more than 1 per cent of all of the cases of osteomyelitis in most of the statistics. The diagnostic difficulty in this 4-year-old female patient arose following incision for traumatic myositis of the thigh. She had recurrence of high fever, dullness, and absence of breath sounds over the right lung field, and roentgenographic examination revealed total opacity of the right lung field. She was erroneously treated for pyothorax, although thoracentesis at another hospital did not yield exudates. On careful examination, the right middle and lower lungs were collapsed, as demonstrated by bronchography. Surgery revealed osteomyelitis of the 3rd to 6th ribs, which were resected; the lungs were normal without pleural adhesions. She made an uneventful recovery. The differential diagnosis, causative agent, and the primary focus leading to costal osteomyelitis are discussed.—I. TATENO

An Immunologic Approach to the Pneumoconioses. P. GROSS*. *AMA Arch Industr Health*, March, 1960, 21: 228–232. (*Industrial Hygiene Foundation, Pittsburgh, Penn.)

Evidence is presented in favor of an immunologic concept of the mechanism underlying not only silicosis but also the pneumoconioses in general, particularly those caused by certain so-called "inert" dusts. Much of this evidence relies on the observed synergism between dust and infection as found in the tuberculopneumoconioses. Here it is assumed that a reciprocal enhancement of immunologic responses to dust and infection occurs. The most formidable support to an immunologic concept of silicosis has come from a group of Italian investigators headed by Vigliani. These workers found an increased γ-globulin content in the blood of some silicotic workers. Later, analysis of the hyaline material in silicotic nodules was shown to consist in large part of β- and γ-globulin. This finding had strong immunologic implications. Evidence was also presented that finely divided silica may enhance significantly an immunologic response to bacteria. Vigliani and Pernis believe silicosis to be a disease of auto-immunity. The antigen, according to these authors, is not a protein denatured by contact with the surface of quartz crystals; instead, the antigen is believed to consist of lipoproteins formed within the quartz-containing macrophages as a result of retrogressive changes. On the basis of this immunologic concept, tuberculosilicosis is explained as a reciprocal, nonspecific enhancement of immunologic responses.—T. H. NOEHREN

Artificial Hibernation in the Treatment of Pneumorrhagia (in Roumanian). L. BRAND*, G. MUTU, and A. COSTEA. *Ftiziologia*, May–June 1959, 3: 247–250. (*Sanatoriu Moroeni, Roumania)

When all other attempts failed to control massive pulmonary hemorrhage in 2 patients, they were successfully treated with artificial hibernation induced and maintained for several days by infusion of a phenothiazine derivate in addition to sedatives.—Z. VIRÁGH

Protamine Sulfate as a Hemostatic in Pneumorrhagia (in German). R. AMANN* and R. WOLFF. *Klin Wschr*, December 15, 1959, 37: 1279. (*Universität Frankfurt, a.M., Germany)

A prompt hemostyptic effect was observed in severe pulmonary hemorrhages following the slow intravenous injection of 10 ml. of 1 per cent protamine sulfate solution. The treatment was successful in all 46 instances tried (13 patients): 10 had exudative cavitary tuberculosis, 2 had bronchiectasis, and 1 patient had a tumor. The injection was administered in a 2-minute period without serious side effects.—Z. VIRÁGH

The Problem of Idiopathic Spontaneous Pneumothorax (in German). A. SATTLER*. *Beitr Klin Tuberk*, July, 1959, 120: 370–376. (*Kaiserstrasse 83/7, Vienna VII, Austria)

The possibility is argued affirmatively that spontaneous pneumothorax may develop not only by perforation of the visceral pleura but also by

molecular diffusion of air into the intrapleural space.—Z. VIRÁGH

Asymptomatic Pulmonary Alveolar Proteinosis. W. FURST*, B. BELL, and G. IRONS. *Amer J Med*, March, 1960, 28: 453–457. (*Albert Einstein College of Med., N. Y., N. Y.)

A case of pulmonary alveolar proteinosis is described, and corroborative data including representative roentgenograms and photomicrographs of the biopsy specimen of the lung are presented. This patient, in contradistinction to others described, was and is totally asymptomatic. He has no dyspnea, cough, or other symptoms. If a film of the chest was not required as part of a routine physical examination, his disease, for the present, would not have been detected. —T. H. NOEHREN

Pulmonary Alveolar Proteinosis. W. FRAIMOW*, R. CATHCART, J. KIRSHNER, and R. TAYLOR. *Amer J Med*, March, 1960, 28: 458–467. (*Jefferson Med. College, Philadelphia, Penn.)

A case is presented of pulmonary alveolar proteinosis followed up with serial biopsies of the lung performed over a 2½-year period. Extensive pulmonary function studies during that period are included, with a correlation of the pathologic and physiologic findings. The patient at the peak of his illness exhibited marked pulmonary findings which have shown a marked improvement over the follow-up period. This has been accompanied by progressive improvement in his clinical status to the point that he is now symptom-free. The ultimate prognosis must remain guarded, however, because of the obscure etiology of the disease and present lack of knowledge as to its course (after authors' summary).—T. H. NOEHREN

The Pathologic Effects of Smoking Tobacco on the Trachea and Bronchial Mucosa. K. P. KNUDTSON*. *Amer J Clin Path*, April, 1960, 33: 310–317. (*V. A. Hosp., Seattle, Wash.)

One hundred and fifty lungs removed at autopsy were examined by means of the Swiss roll method. The changes noted were correlated with the history of smoking, age, occupation, and site of residence. Normal mucous membranes were found in 50 per cent of the lungs of non-smokers, as compared to 20 per cent in those of heavy smokers. The carina was the most frequent site of metaplasia. Age, occupation, and the site of residence had no appreciable relation to the changes in the bronchial mucosa.—E. DUNNER

The Diagnosis of Toxoplasmosis (in German). O. THALHAMMER*. *Wien Med Wschr*, June 7, 1958, 108: 499–503. (*Universitäts-Kinderklinik, Vienna, Austria)

Toxoplasmosis is a generalized infection; pathogenicity for man is relatively small. Spontaneous healing is not infrequent. The clinical picture is protean; it may cause pneumonitis. The diagnosis of toxoplasmosis can be established by various testing methods, such as the Sabin-Feldmann and the Sabin-Warren-Russ complement-fixation reactions and the Frenkel skin test. Every patient with interstitial pneumonia of unknown etiology should be examined for toxoplasmosis.—Z. VIRÁGH

Tuberculosis and Mycosis (in German). E. UEHLINGER*. *Schweiz Z Tuberk*, No. 5, 1959, 16: 347–358. (*Pathologisches Institut der Universität, Schmelzbergstr. 12, Zürich, Switzerland)

The case history is presented of a 56-year-old man with tuberculous septicemia, treated with streptomycin, broad-spectrum antimicrobials, and steroids. Roentgenograms showed infiltrations in both lungs, acid-fast bacilli were not demonstrated in the bronchial secretions, and repeated cultures of blood showed no growth of any organisms. The patient died on the 34th day after admission. At autopsy, necrosis was found in the lungs, liver, spleen, adrenals, and bone marrow, and wide-spread caseation was present in the tracheobronchial lymph nodes. All of the extrapulmonary caseating foci—including the tracheobronchial lymph nodes—contained virulent tubercle bacilli. The lungs were free of *M. tuberculosis* but, in the necrotized tissue, Aspergillus was identified.—Z. VIRÁGH

Carcinoma of the Parathyroid Gland with Pulmonary Metastases and Cardiac Death. A. RAPOPORT*, A. SEPP, and W. BROWN. *Amer J Med*, March, 1960, 28: 443–451. (*U. of Toronto, Ontario, Canada)

The case is presented of a 20-year-old woman with parathyroid carcinoma and pulmonary metastases. This is believed to be the ninth case of parathyroid carcinoma with visceral metastases reported in the literature.—T. H. NOEHREN

Leiomyoma of the Lung; A Case Report (in Japanese). S. HAYASHI*, T. YUASA, H. KAMEMORI, M. MORI, and T. KURODA. *Jap J Thor Surg*, April, 1960, 13: 290–293. (*Juntendo U., Tokyo, Japan)

A benign leiomyoma of the lung is a rare condition, and none has before been reported in Japan. The writers report the case of a 49-year-old female with no subjective symptoms in whom a casual roentgenographic examination of the lung revealed a coin lesion in the right lower lung field medially. A surgically removed tumor was in the

S_8 segment of the lower lung adherent to the bronchus. Histologically it was a benign leiomyoma, and there was no sign of malignant change although she had undergone hysterectomy 15 years previously because of leiomyoma of the uterus. The patient had an uneventful recovery. It is concluded that the benign leiomyoma of the lung originally developed independent of that of the uterus.—I. TATENO

Multiple Myeloma Manifested as a Problem in the Diagnosis of Pulmonary Disease. E. FAVIS*, H. KERMAN, and W. SCHILDECKER. *Amer J Med*, February, 1960, 28: 323–327. (*Daytona Beach, Florida)

A case is reported of multiple myeloma which presented dominant pleuropulmonary manifestations. The pulmonary pathology was probably due to pleural plasmocytomas, with subpleural and pulmonary parenchymal myelomatous involvement. Multiple myeloma was first suspected when excessive rouleaux formation was reported in a peripheral blood smear. Further confirmatory evidence was given by the typical electrophoretic pattern of the serum proteins. The classic roentgenographic findings of multiple myeloma were found in the left scapula, right femur, ischium, and skull. The presence of numerous plasma cells in the pleural fluid and bone marrow was diagnostic.—T. H. NOEHREN

TUBERCULOSIS, PULMONARY

An Exceptional Pathologic Association: Tuberculosis and Pulmonary Adenomatosis (in Italian). G. SARTORI*, D. ZANNONI, and L. ABATE. *Riv Pat Clin Tuberc*, No. 2, 1959, 32: 242–264. (*Ist. C. A. Pizzardi, Bologna, Italy)

A description is given of a case in which a pulmonary adenomatosis was found associated with a chronic form of pulmonary tuberculosis. The adenomatosis arose when the lung was already affected by tuberculosis. The anatomic and histologic aspects of the lung are described in detail. It is suggested that the chronic inflammatory processes may have caused the neoplastic differentiation of the broncho-alveolar epithelium.
—G. CASTELNUOVO

A Stratigraphic Study of the Azygos Vein in Pulmonary Tuberculosis (in Italian). G. MARTINOTTI* and R. MOTTA. *Riv Pat Clin Tuberc*, No. 1, 1959, 32: 43–56. (* Osp. Civ. S. Croce, Cuneo, Italy)

An enlarged and laterally displaced azygos vein was evident in almost all forms of pulmonary tuberculosis. A description is given of the most common and frequent morphologic variations which occur in this vein in cases of affections of the pulmonary parenchyma.—G. CASTELNUOVO

Secondary Tuberculous Infection of Pulmonary Cysts (in German). R. SCHAUB* and D. KLAUS. *Beitr Klin Tuberk*, September, 1959, 120: 415–427. (* Med. Univ.-Klinik and Poliklinik, Tübingen a.N., Germany)

On the basis of two case histories described, it is suggested that a secondary tuberculous infection is possible in cystic pulmonary disease.
—Z. VIRÁGH

Gastritis in Tuberculous Patients: An Anatomic-Histologic Study (in Italian). I. ABATE* and D. ZANNONI. *Riv Pat Clin Tuberc*, No. 1, 1959, 32: 113–139. (* Ist. C. A. Pizzardi, Bologna, Italy)

The histologic changes in the stomachs of 40 patients with severe cavitary tuberculosis are reported. An alteration of the mucosa accompanied by degenerative changes, modifications of the cellular types, hypoadenia, adenometaplasia, hypertrophy of the muscular layer, and alteration of the intramural nervous elements are the most frequent changes which occur in these patients. Various considerations on the pathogenesis of these alterations are reported.—G. CASTELNUOVO

On the Pathologic Processes Produced by Paratubercle Mycobacteria in Men: Observations on Two New Cases (in Italian). B. MARIANI*, A. BISETTI, and G. BROCCHI. *Riv Pat Clin Tuberc*, No. 1, 1959, 32: 91–92. (* U. of Modena, Italy)

A brief preliminary report is given on 2 patients with serious manifest tuberculous-like processes from which unclassified (atypical) mycobacteria were isolated. These mycobacteria were very slightly pathogenic for guinea pigs, while they were highly resistant to PAS and to streptomycin in 1 case, and highly resistant to PAS but not to streptomycin in the other.—G. CASTELNUOVO

Studies on the Levels of Serum Tryptophane in Pulmonary Tuberculosis. First Report (in Japanese). H. KAKINOKI*. *Kekkaku*, April, 1960, 35: 260–264. (* School of Med., Hokkaido U., Sapporo, Japan)

The serum levels of tryptophane were determined in 236 patients with pulmonary tuberculosis, and the statement of Undritz (1933) was confirmed. The levels were higher in patients with far and moderately advanced lesions than in normal persons. The highest value was obtained

in the first group. A close correlation was found between the elevated serum tryptophane levels and the erythrocyte sedimentation rate or the various serum colloid reactions. They decreased after administration of streptomycin or isoniazid. Administration of vitamin B_6 simultaneously with isoniazid prevented the decrease of serum tryptophane levels. They were not influenced by the administration for 1 month of PAS or anthranilic acid alone.—I. TATENO

Transactions of the Convention of the German Tuberculosis Association. *Beitr Klin Tuberk*, July, 1959, 121: 1–268.

This is a collection of 26 original papers presented and discussed; also, the colloquies held on 13 subjects at the convention in Hamburg, Germany, on September 16–19, 1958.—Z. VIRÁGH

Effect of Infectious Diseases on the Course of Medically Treated Tuberculosis in Children (in German). H. W. KIRCHHOFF*. *Tuberkulosearzt*, February, 1960, 14: 92–101. (* Landeskinderklinik, Neunkirchen-Kohlhof/Saar, Germany)

While on antimycobacterials, 182 tuberculous children contracted infectious diseases (measles, mumps, whooping cough, et cetera). There were no cases of hematogenous or bronchogenic spread of the disease but, in some instances, enlargement of the hilar or paravertebral lymph nodes, perihilar infiltrations, and opacities occurred. The clinical course of the disease was not seriously affected. These observations indicate that antimycobacterials are capable of preventing, or at least minimizing, the serious complications that are apt to develop in tuberculous children who contract an intercurrent infectious disease.
—J. HAAPANEN

TUBERCULOSIS, NONPULMONARY

Acute Disseminated Tuberculosis with Hematological Symptoms and Corticosteroid Therapy. O. H. IVERSEN* and E. OFSTAD. *Acta Med Scand*, March 30, 1960, 166: 291–295. (* Institute for General and Experimental Pathology, Oslo, Norway)

Five patients with uncharacteristic conditions involving hematologic symptoms were treated with corticotropin or cortisone. Autopsy revealed disseminated tuberculosis in each case, with multiple necrotic areas, slight development of specific granulation tissue, and no fibrosis.
—E. DUNNER

Genital Tuberculosis in Ethiopian Women (in German). A. HUBER*. *Wien Med Wschr*, September 26, 1959, 109: 729–735. (* P. O. Box 1159, Addis Ababa, Ethiopia)

Of 1,000 women examined in 4 years, genital tuberculosis was found in 35 (3.5 per cent). It is believed that this number is in reality about twice as great; consequently, it is considerably higher than that reported from other countries. The diagnosis was established by biopsy of the endometrium. Tubercle bacilli were not recovered in any of the cases. Most of the women reported for examination because of sterility. None of those who underwent antituberculous treatment became pregnant.—Z. VIRÁGH

The Results of Catamnestic Examinations and the Actual Problems of Tuberculous Meningitis (in German). A. LIENER*. *Beitr Klin Tuberk*, July, 1959, 120: 315–330. (* Landeskrankenhaus für Tuberkulose Natters, Post Mutters, Tirol, Austria)

The case histories were analyzed of 211 patients (158 children and 53 adults) with verified tuberculous meningitis. It is not easy to determine the onset of the disease; tuberculous meningitis was sometimes revealed at autopsy of patients known to have its symptoms only in the terminal stage or not at all. Chest roentgenograms and the leukocyte-lymphocyte ratio may help in establishing the diagnosis. Only 40 per cent of the cases showed the classic picture of the disease. In 3 patients, the disease developed under treatment with isoniazid and streptomycin for pulmonary tuberculosis; a 9-month-old infant was diagnosed as having tuberculous meningitis while under prophylactic treatment with isoniazid. Streptomycin was administered both intrathecally and intramuscularly in all cases. Among the post-treatment damages were: complete deafness in 3 patients (all from the period when only streptomycin was used); in 5 patients arachnitis was diagnosed; 3 patients had purulent meningitis (healed completely); and a 15-year-old girl developed a spinal epidermoid of traumatic etiology. Of 7 gravid women, 1 died. Human tubercle bacilli were identified in all but 2 cultures, which were of the bovine type.—Z. VIRÁGH

The C-Reactive Protein Test in Osteoarticular Tuberculosis (in Italian). G. COSTA* and P. ABBAMONTE. *Riv Pat Clin Tuberc*, No. 2, 1959, 32: 197–202. (* U. of Genova, Italy)

The C-reactive protein test was performed on 66 patients with osteoarticular tuberculosis. The results obtained show that this test is useful in supplying information on the progress and evolution of the disease, and as an indication of the efficacy of the therapy applied.—G. CASTELNUOVO

Surgical Treatment of Paralysis in Tuberculous Spondylitis (in Hungarian). S. Széman*, T. Riskó, and P. Móritz. *Tuberkulozis*, September, 1959, 9: 207–209. (* Állami Fodor József Tbc. Gyógyintézet, Budapest, Hungary)

Among 589 patients with tuberculous spondylitis, 42 (7.1 per cent) had serious paralysis of spinal cord origin. In 15 patients, costovertebrotomy-spondylodesis was performed, and 1 patient was treated with laminectomy. Surgery was done parallel with antimicrobial treatment. Surgical intervention must be selective, determined by the pathologic picture of the process.—Z. Virágh

UPPER RESPIRATORY TRACT DISEASE, VIRAL

Influenza-like Illness in Naval Personnel, Spring, 1959. P. K. Fraser*, L. A. Hatch, L. G. H. LeClercq, and J. M. R. Forster. *Amer J Med Sci*, March, 1960, 239: 320–323. (* Royal Naval Hosp., Haslar, England)

Serologic studies on an outbreak of acute upper respiratory illness among British naval personnel early in 1959 showed that most of the hospitalized patients had been infected by influenza A, B, or adenovirus. Pneumonia was the chief complication in each of these groups of infections. One death occurred and *Staphylococcus pyogenes* and influenza A2 virus were isolated from the lung tissue. Paired serum specimens taken from recruits at 3-month intervals did not reveal all of the infections experienced. Additional significant rises in titer against one or more antigens were found when paired serum specimens taken from the acutely ill within the period were tested.
—W. J. Steininger

THORACIC SURGERY

The Reliability of Tissue Diagnosis of Pleurisy: A Preliminary Report. J. Richert*, J. Wier, J. Salyer, and J. Beyer. *Ann Intern Med*, February, 1960, 52: 320–325. (* Fitzsimons Army Hosp., Denver, Colorado)

Pleural biopsy has provided a convenient and reasonably safe method of differentiating granulomatous from nongranulomatous pleurisy. Bacteriologic confirmation of tuberculosis was obtained in ⅔ of the 24 granulomatous cases studied. Preliminary follow-up has not shown reactivation of tuberculosis in the 22 nongranulomatous patients who were discharged from the hospital without prolonged antituberculosis drug therapy. If future follow-up confirms this trend, it will indicate that tissue diagnosis of pleurisy is a reliable means of selecting the patients who should be treated for tuberculosis. The most reliable biopsy technique is the full thoracotomy, but it seems likely that thoracotomy with the limited incision would give satisfactory results if properly performed. Inspection and palpation of the lung were of little diagnostic value in this series. In the future, needle biopsies which show granulomas will be considered to be adequate proof of the diagnosis, and in these cases the more extensive surgical procedures will not be done unless a therapeutic decortication is needed.
—T. H. Noehren

Significance of and Indications for Selective Bronchography (in Czech). C. Šimeček*. *Rozhl Tuberk*, November, 1958, 18: 653–656. (* District Hosp., Olomouc, Czechoslovakia)

Special endobronchial catheters manufactured according to the specifications of the author were used in this study. The selective contrast filling serves, first, as a kind of introduction to the usual bronchographic examination because it makes visible even the poorly ventilated areas; and second, it is suitable for the mere localization of a pathologic process, or it can be used as a supplement to previous incomplete bronchographic examinations. The contrast filling obtained by this technique gives better results than normal bronchography in cases in which various special problems are investigated; for example, changes of the draining bronchus from tuberculous cavities, or disintegrating carcinoma.—J. Ilavsky

Management of Nonpenetrating Injuries of the Chest. C. C. Craighead* and B. A. Glass. *JAMA*, March 12, 1960, 172: 1138–1142. (* Louisiana State U., New Orleans)

Uncomplicated fractures of the rib are treated with analgesics and, frequently, intercostal nerve block, to control pain. Roentgenographic examination is repeated after about 6 hours because late development of pneumothorax, hemothorax, or hemopneumothorax can occur, even after several days. In 13 of 166 patients with nonpenetrating injuries of the chest, subcutaneous emphysema occurred without demonstrable pneumo- or hemothorax. When pneumo-, hemo-, or hemopneumothorax is demonstrated, the treatment procedure should be directed toward obtaining symphisis of the pleural surfaces. This may be accomplished by aspiration or tube thoracotomy whenever the former method is not successful. Mediastinal injuries may result in myocardial infarction which should be treated accordingly. The treatment of stove-in (flail) chest is an emergency and consists of immediate stabilization by sand bags and, if necessary, traction with Bigelow screws attached

to the sternum, traction from the pectoral muscles, or a combination of both traction procedures. Tracheotomy often has to be done in order to keep the tracheobronchial tree free from secretions. —H. Abeles

The Treatment of Maximal Lesions. I. Extramusculoperiosteal Collapse (in Serbo-Croatian). T. Furlan*, B. Korac, J. Mesic, and S. Goldman. *Tuberkuloza*, No. 4, 1958, 10: 187–192. (* Tuberculosis Institute, Golnik, Yugoslavia)

Extramusculoperiosteal pneumonolysis was performed in 98 patients with far advanced pulmonary tuberculosis in the period from 1953 to 1957. A follow-up study, which was conducted at the end of 1957, gave the following results: 9 dead, 27 with and 38 without sputum positive for tubercle bacilli, and no reply from 24. Only 1 case is described of immediate death due to perforation of the cavity into the free pleural cavity in which resection was impossible because of respiratory insufficiency. The therapeutic indications and the aim of the operation are discussed. The authors conclude that resectional therapy cannot be considered the only means of surgical treatment in far advanced pulmonary tuberculosis. In addition to resection, the authors make use of intra- as well as extrapleural, extramusculoperiosteal, and thoracoplastic collapse. It is believed that extramusculoperiosteal collapse is more effective than the collapse achieved with thoracoplasty; it preserves the respiratory capacity and is, during the first few weeks, still reversible. The collapse is maintained by refills of air or liquid paraffin.—D. R. Matiasevic

Circulatory Changes due to Open Pneumothorax in Surgical Patients. T. Li*, H. Rheinlander, and B. Etsten. *Anesthesiology*, March–April, 1960, 21: 171–177. (* Tufts U. School of Med., Boston, Mass.)

An evaluation in anesthetized man was carried out to determine the effects upon circulation of an open pneumothorax, controlling as rigidly as possible the patient's position, the anesthetic agent, the depth of anesthesia, the alveolar ventilation, the mean airway pressure, the arterial oxygen saturation, the arterial P_{CO_2}, and the surgical manipulation. The method was employed in 10 patients who were free of cardiac disease, and it is discussed in detail. Anesthesia was maintained with cyclopropane. No change was noted in the arterial blood pressure or heart rate, but the cardiac output was reduced and the total peripheral resistance increased. The reduced cardiac output was correlated with a decrease in stroke volume and intrathoracic pressure. A decrease in lung size, an increase in pulmonary vascular resistance, and the influence of atmospheric pressure on the mediastinal structures probably are the factors responsible for the decrease in cardiac output. Mention is made that blood loss, surgical retraction, increased airway resistance, inadequate pulmonary ventilation, and deep anesthesia could singularly or in combination act as factors to further reduce cardiac output.—E. Shabart

The Postpneumonectomy State. B. Burrows*, R. Harrison, W. Adams, E. Humphreys, E. Long, and A. Reimann. *Amer J Med*, February, 1960, 28: 281–297. (* U. of Chicago School of Med., Illinois)

Clinical and physiologic observations in 36 post-pneumonectomy patients are presented. In the majority of cases there was a progressive overinflation of the remaining lung during the first postoperative year, but no significant decrease in exercise tolerance. Pulmonary function tests and cardiac catheterization studies revealed a decrease in pulmonary diffusing capacity and an elevated right heart pressure on exertion. These responses are believed to represent the expected pattern for a single normal remaining lung. There was no evidence of destructive changes in the remaining lung in most subjects, even after prolonged pulmonary overinflation. Nine patients demonstrated more severe respiratory symptoms. In 4 instances these may be ascribed to a complicating cardiac or pulmonary disorder. The remaining 5 patients showed evidence of chronic obstructive emphysema which is believed to have developed independent of, and in 4 cases, prior to, the pulmonary resection. The physiologic abnormalities in these patients are certainly aggravated as a result of the removal of functioning lung tissue.

Those patients with an abnormal remaining lung showed resting pulmonary hypertension and, in a few instances, clinical evidence of cor pulmonale. The perfusion function of the lungs is particularly sensitive to pulmonary resection; preoperative tests applicable to this problem are discussed. The effects of pneumonectomy on pulmonary artery pressure and pulmonary diffusing capacity are contrasted with the reported effects of exertion, both conditions resulting in an increased blood flow per unit of lung. An active vasomotor effect of exercise on pulmonary vasculature is believed to exist and to explain the differences in response of the pulmonary vasculature to these two stimuli (Authors' summary).—T. H. Noehren

Healing of the Bronchial Stump following Lung Resection in Tuberculosis (in Czech). J. Kropáček*, J. Blumberg, and Z. Smékal. *Rozhl Tuberk*, November, 1958, 18: 635–641. (* Masaryk U., Brno, Czechoslovakia)

The authors analyzed and treated by resection 131 patients with pulmonary tuberculosis. Five patients died. One of them and another patient from the surviving group developed bronchial fistulas. Two patients had early relapses of tuberculosis. In 123 cases the results were favorable and the sputum became negative for tubercle bacilli. Bronchoscopy was performed in 101 patients 4 to 6 months later. A pathologic focus was detected in 51 patients, including 43 in whom the stitches were spontaneously eliminated. After operation, temporarily positive sputum was found in 29.4 per cent of the patients in this group, while positive sputum was present in only 10.7 per cent of the patients with well-healed resections. Granulations which form around nonabsorbable sutures cause problems unless such sutures are expectorated or endoscopically removed. Long-term chemotherapy contributed considerably toward proper healing.—J. Ilavsky

ROENTGENOGRAPHY

Bronchographic Aspects of Chronic Bronchitis (in French). P. Lageze*, P. Galy, R. Touraine, Ch. Chassagnon, and J. Ternamian. *Schweiz Z Tuberk*, No. 5, 1959, 16: 279–290. (* Service de Bronchopneumologie, Hospital Edouard-Herriot, Lyon, France)

The authors analyzed the bronchograms of 56 patients of various ages and both sexes, and concluded that chronic bronchitis is not a diffuse but a localized disease, very often unilateral. It may cause changes in the cartilage of the bronchi or bronchioli.—Z. Virágh

Pathognomonic Signs of Chronic Bronchitis. V. Oliva*, C. Spradley, and S. Williams. *Amer J Roentgenol*, February, 1960, 83: 274–278. (* U. S. Naval Base, San Diego, Calif.)

The diagnosis of chronic bronchitis can be made with roentgenographic and bronchographic evidence of: bronchial gland dilatation (bronchial adenolectasis); bronchiolectasis (bronchiolar diverticulosis); distortion of bronchial walls with abnormal changes in caliber on inspiration and expiration; and coincident emphysema and fibrosis. The first two of the above manifestations are considered by the authors to be roentgenographically pathognomonic of chronic bronchitis. A case demonstrating both bronchiolar diverticulosis and bronchial adenolectasis is presented (after authors' summary).—T. H. Noehren

The Roentgenographic Appearance of Eosinophilic Lung (Tropical Eosinophilia). F. Khoo* and T. Danaraj. *Amer J Roentgenol*, February, 1960, 83: 251–259. (* General Hosp., Singapore, Malaya)

This paper presents a description of the roentgenographic appearance of eosinophilic lung and the changes following treatment from a study of 550 patients seen in Singapore. Although Singapore has a predominantly Chinese population (77.6 per cent), the disease is seen most frequently in Indians (79.3 per cent), Chinese being less commonly affected, and Europeans very rarely. Cases have been recorded in children and in the elderly, but the peak incidence is found in the age group of 20 to 40 years. Neither sex nor occupation seems to be an important etiologic factor. The presenting symptom is chronic cough, which is most frequent and severe at night, occurring in paroxysms of a few minutes with mucoid or mucopurulent sputum which is sometimes streaked with blood. The paroxysms may be severe enough to force the patient to sit up in bed, and sleep is badly disturbed. A feeling of suffocation is present after each bout of coughing, and breathlessness is at times so severe and prolonged as to resemble bronchial asthma or even status asthmaticus. There is relative freedom from cough during the day, but there is considerable fatigue. Low fever may occur for varying periods, and some loss of weight is usually present. The abnormal physical signs are confined to the chest, and consist of coarse crepitations and scattered rhonchi heard over the bases of the lungs; bronchial spasm may be present in severe cases. There is neither splenomegaly nor lymphadenopathy. A persistent massive eosinophilic leukocytosis (usually more than 5,000 eosinophils per cu. mm. and, less often, between 3,000 and 5,000 eosinophils) is always present and is an essential feature of the disease; the peripheral blood picture is otherwise normal. The erythrocyte sedimentation rate is usually elevated and is a feature differentiating eosinophilic lung from allergic bronchial asthma, which is often simulated.—T. H. Noehren

Idiopathic Pulmonary Hemosiderosis in Adults. S. Bronson*. *Amer J Roentgenol*, February, 1960, 83: 260–273. (* V. A. Hosp., Atlanta, Georgia)

In idiopathic pulmonary hemosiderosis, phagocytized and free hemosiderin appear in the alveoli, the walls of the alveoli and capillaries and, also, in the bronchial walls and mediastinal lymph nodes; characteristically, no deposition of hemosiderin is found in other areas of the organism (except occasionally in the liver and spleen). The derangement in the circulation, apparently in the terminal pulmonary vascular structures, leads to

a widespread serious diapedesis or hemorrhage from the small capillaries; as a result, hemosiderosis of the lungs takes place. The roentgenographic pattern is similar to that of miliary tuberculosis, sarcoidosis, carcinomatosis, and the pneumoconioses. The clinical importance of differentiating between these diseases and idiopathic pulmonary hemosiderosis becomes more urgent with the increasing number of cases being described. Joseph *et al.*, in 1958, found 56 cases of idiopathic pulmonary hemosiderosis in the world literature, 10 of which are included in the present collection of 37 adult cases. Wynn-Williams and Young reported 1 new case in an adult, and found 15 cases of adults with idiopathic pulmonary hemosiderosis in the literature. Shoeniger *et al.*, in 1958, found in the literature 60 cases in adults and children. Boyd collected 26 adult cases from the literature and reported 3 new cases in adults, making a total of 29. In this paper, a new case of idiopathic pulmonary hemosiderosis is reported, in a 27½-year-old white male. In addition, 37 cases in adults 16 years or older were found in the world literature. Pertinent clinical and roentgenographic data are reviewed.—T. H. NOEHREN

Epidemic Pulmonary Histoplasmosis. Roentgenographic Findings. D. BABBIT* and B. WAISBREN. *Amer J Roentgenol*, February, 1960, 83: 236–250. (* Milwaukee Hosp., Wisconsin)

This is a report of the roentgenographic findings in 19 cases of epidemic histoplasmosis, due to a single source of *Histoplasma capsulatum*, occurring over a span of 3 months. A group of men became infected while performing work associated with the construction of a new house on a vacant lot, in the community of Walworth, Wisconsin. They were engaged in digging ditches for water mains and sewer lines. The duration of exposure varied from ½ hour to 8 hours. The incubation periods could be determined accurately, and varied from 7 to 16 days. The cause of the outbreak was established by the isolation of *H. capsulatum* from 2 of the cases. The other cases were diagnosed by complement-fixation tests. The general clinical pattern was characterized by the acute onset of malaise, fever, weakness, and headache in 12 of the 19 cases. In 5 of the remaining 7 cases, a prodromal period marked by malaise and weakness was evident before the onset of fever and other symptoms. The 2 additional cases were marked by malaise, weakness, muscular aches, and cough, but without known fever or other symptoms. The fever varied between 100°F. and 104°F., and was present in all but 2 cases. Chills were frequent, and diaphoresis out of proportion to the fever present was noted. Cough, pain in the chest, and dyspnea were other symptoms.

In acute epidemic histoplasmosis, the illness and the chest lesions may vary from very mild to extremely severe, depending apparently on the degree of exposure. The roentgenographic findings are reported. In the very mild to mild cases, lymphadenopathy with minimal pulmonary nodulation and infiltration was seen. In the moderate and severe cases, the degree of hilar lymphadenopathy was more marked, and the nodulations and pulmonary infiltrations became more extensive with coalescence.—T. H. NOEHREN

Segmental Localization of Pulmonary Disease. G. PARKER*, H. STURTEVANT, J. REED, and R. FLAHERTY. *Amer J Roentgenol*, February, 1960, 83: 217–226. (* U. S. Air Force Hosp., Lackland Air Force Base, Texas)

Segmental localization of pulmonary disease can be accurately accomplished in practically all instances by utilizing only the postero-anterior chest roentgenogram. Accurate localization of the pulmonary infiltrate depends upon a knowledge of the distribution of the segmental bronchi and the surface anatomy of the segments in relation to adjacent intrathoracic structures. The authors demonstrate some variance in appearance of the bronchopulmonary segments compared with earlier descriptions. They are of the opinion that there is less anatomic distortion with acute pneumonia than with other pulmonary diseases, and believe that the diagrams accurately depict the bronchopulmonary segments.
—T. H. NOEHREN

Vascular Measurements of Smokers and Nonsmokers. Differences Seen in Posteroanterior Roentgenograms Made with Patients Standing Erect. J. PAGAN-CARLO*. *JAMA*, December 19, 1959, 171: 2182–2184. (* Touro Inf., New Orleans, La.)

Plain anteroposterior roentgenograms of the chest were used to obtain micrometric measurements of the caliber of the pulmonary blood vessels of 694 smokers and nonsmokers. The vessels in the main hilar zone of heavy smokers were significantly larger than those of nonsmokers, possibly due to the vasoconstrictive effect of nicotine on the smaller radicles of the pulmonary arterial tree, resulting in some degree of pulmonary hypertension.—H. ABELES

Misleading Thoracic Roentgenograms. C. HODGSON*, J. CALLAHAN, A. BRUWER, and A. BULBULIAN. *AMA Arch Intern Med*, February, 1960, 105: 277–300. (* Mayo Clinic, Rochester, Minn.)

Roentgenograms of the thorax in certain cardiovascular conditions may simulate those associated with diseases of the lungs, bony thorax, or mediastinum. It is important to be aware of these similarities, which may be remarkable. Roent-

genographic shadows may be produced that look very much like those characteristic of a different disease. The recognition of the real cause of these roentgenographic changes may allow treatment of an apparently hopeless condition, or prevent an unnecessary operation. This article presents examples of such misleading roentgenograms under the following categories: shadows produced by abnormal aortic contours, shadows suggesting intrathoracic tumor, shadows produced by intrathoracic fluid, and shadows of diverse origin and complexity.—T. H. NOEHREN

CHEMOTHERAPY

Pathogenic Staphylococci Isolated at Boston City Hospital in 1958: Phage Types and Antibiotic Susceptibility. M. FINLAND*, H. A. HIRSCH, and G. WALLMARK. *AMA Arch Intern Med*, March, 1960, 105: 383–397. (* Boston City Hosp, Mass.)

Phage typing and susceptibility tests to 28 antimicrobials were carried out on strains of pathogenic staphylococci isolated from outpatients and hospitalized patients at the Boston City Hospital during the last 3 months of 1958. The proportions of these strains resistant to penicillin, streptomycin, tetracycline, and erythromycin were slightly less than among those tested in the hospital in 1955, due to the inclusion in this study of strains from outpatients not treated with antimicrobials. Resistant strains were much more frequently isolated from patients after they had been in the hospital for more than a week and treated with antimicrobials. Strains with the phage pattern identified as 80/81/KS6, although accounting for less than 1/8 of the total, included the highest proportion resistant to penicillin and streptomycin and the lowest resistant to erythromycin. Strains lysed by phages of Group III were much more frequently resistant to erythromycin. Successive isolations of strains of the same phage type showing increased resistance to any antimicrobial were usually associated with administration of that drug to the patient, but this was observed only infrequently.—W. J. STEININGER

The Sensitivity of Hemolytic Staphylococci to a Series of Antibiotics. II. A Three-Year Progress Report. R. G. PETERSDORF*, M. C. ROSE, H. B. MINCHEW, W. R. KEENE, and I. L. BENNETT, JR. *AMA Arch Intern Med*, March, 1960, 105: 398–412. (* Johns Hopkins Hosp., Baltimore, Md.)

Sensitivity studies on 300 strains of hemolytic staphylococci show that, although many are resistant to penicillin, nearly 50 per cent of the strains are susceptible to 50 units of penicillin per ml. Among the newer agents, vancomycin and kanamycin are potent bactericidal agents, while novobiocin, oleandomycin, ristocetin, and leukomycin inhibit but do not kill most strains. There has been no increase in resistance to chloramphenicol and erythromycin during the past 3 years. Organisms lysed by bacteriophage 81 are uniformly resistant to high concentrations of penicillin and tetracycline, and slightly more resistant to most other agents. In general, tube dilution sensitivities are in good agreement with routine discs. Finally, a program is presented for the treatment of staphylococcal disease which emphasizes that hospital-acquired infections should be treated with different agents than infections not acquired in hospital.—W. J. STEININGER

The Susceptibility of Staphylococci to Chloramphenicol: A Survey of Experimental and Clinical Experience. M. W. FISHER*. *AMA Arch Intern Med*, March, 1960, 105: 413–423. (* Parke, Davis & Co., Detroit, Mich.)

Experimental and clinical observations reveal that there may be a unique relationship between chloramphenicol and staphylococci with respect to an infrequency of resistant strains. These conclusions have been reached: (*1*) The actual incidence of staphylococci which are truly resistant to chloramphenicol may be exaggerated by certain test methods and criteria. (*2*) Experimentally, resistance to chloramphenicol develops slowly and only to a moderate degree, suggesting an intrinsic inability of staphylococci to acquire chloramphenicol resistance. (*3*) In man, resistant strains occur infrequently and in moderate degree, back-mutating to a state of susceptibility in some instances, and responding to increased dosages of chloramphenicol. (*4*) Chloramphenicol resistance does not appear to be related to the frequency and intensity of use of this drug. When considering the choice of antimicrobial therapy for a staphylococcal infection, the problem of drug resistance can be regarded as minimal for chloramphenicol.—W. J. STEININGER

Therapeutic Resensitization of Tubercle Bacilli That Become Resistant to Chemotherapy (in French). G. DADDI* and M. CORDA. *Rev Tuberc (Par)*, December, 1959, 23: 1181–1189. (* Milano, Italy)

Bacteriologic studies were performed in 1,177 cases of pulmonary tuberculosis every 2–3 months and at each change of medication. The following drug combinations were used: isoniazid-streptomycin; streptomycin-PAS; isoniazid-PAS; isoniazid-cycloserine; and isoniazid-pyrazinamide. In patients originally resistant to isoniazid, streptomycin, and PAS, resistance often disappeared

in the course of continued treatment; this disappearance was called "resensitization." Of the resensitized cases, 18 per cent showed improvement, 75 per cent remained stationary, and only 7 per cent became worse.—V. LEITES

The Fluctuations of Resistance of Tubercle Bacilli in the Course of Treatment of Pulmonary Tuberculosis (in French). E. BERNARD*, B. KREIS, L. VOIVODITCH, and S. PRETET. *Rev Tuberc* (*Par*), December, 1959, 23: 1125–1136. (* Paris, France)

Among 201 patients with pulmonary tuberculosis who showed strains resistant to one or more antituberculous drugs upon admission to the hospital, bacterial resistance was again determined after 3 months of treatment. It was identical with the initial findings in 43.7 per cent; in 16 per cent resistance was increased; it decreased or had disappeared in 40.3 per cent. The reasons for this are varied: (*1*) Technical factors should be excluded and slight fluctuations of resistance should be considered only if confirmed by a second determination. (*2*) The main reason for oscillations of resistance is heterogeneity of strains with different degrees of resistance. In these cases, different groups of bacilli happen to be at a disadvantage in the course of treatment, which determines the new degree of resistance. The therapeutic implications are as follows: (*1*) If only a small fraction of the population of a strain is resistant, treatment should not be interrupted. In these cases, diminution or even disappearance of resistance can eventually be observed; but it is useful to add a new drug to the regimen. (*2*) If a strain is totally resistant, treatment has lost its effectiveness, even if there are apparently favorable variations in the degree of resistance.—V. LEITES

Study of Electro-Encephalograms in 50 Patients with Pulmonary Tuberculosis Treated with Cycloserine (in French). J. LEBASCLE* and J. CHENEBAULT. *Rev Tuberc* (*Par*), December, 1959, 23: 1247–1256. (* Casablanca, Morocco)

A study of 160 electro-encephalograms in 50 patients treated with cycloserine led to the following conclusions: (*1*) Before treatment with the drug was started, 21 patients (42 per cent) had abnormal electro-encephalograms. (*2*) During cycloserine treatment these abnormal findings became accentuated (16 cases), improved (9 cases), and in 15 cases there was modification of response to light stimulus. Worsening of the electro-encelphalogram was observed mainly in older patients, especially men, and in patients with psychiatric disturbance prior to treatment. (*3*) The electro-encephalographic changes under all circumstances were minimal; there was not always a correlation with clinically observed neuropsychiatric manifestations; they did not permit, in the individual case, to foresee and to avoid neurotoxicity.—V. LEITES

Clinical Contribution to the Study of Cycloserine Therapy in Pulmonary Tuberculosis (in Italian). O. BOLONDI*, E. FOCHI RIGNANI, and A. MOSTI. *Riv Pat Clin Tuberc*, No. 2, 1959, 32: 215–224. (* Sanat. Belfiore, Mantova, Italy)

The results are reported on 30 patients with pulmonary tuberculosis who were treated with cycloserine. The drug was administered in gradually increasing doses up to 1 gm. daily for a period of 60 to 240 days; in no case did the total amount of the drug exceed 15–150 gm. Cycloserine was well tolerated even when given for long periods of time, and no serious toxicity ever appeared; in many cases a real improvement in kinesthesis and general condition was obtained. The drug was particularly useful in some recent exudative forms of the disease while, in the cavitary and ulcerous caseous forms, an improvement was noted only during the period of treatment; once treatment was stopped the conditions of the patients worsened.—G. CASTELNUOVO

Cycloserine Treatment in Children and Adolescents (in German). G. PRIMER*. *Tuberkulosearzt*, March, 1960, 14: 163–168. (* Kinderheilstätte, Wangen im Allgäu, Germany)

Twenty-four young persons with pulmonary tuberculosis were treated with cycloserine, 20 mg. per kg. of body weight daily. Cycloserine was inferior to streptomycin and isoniazid, but equal to PAS in therapeutic efficacy. Cycloserine also succeeded in a number of cases in restoring full susceptibility to streptomycin and PAS, but not to isoniazid.—J. HAAPANEN

D-Cycloserine in the Treatment of Pulmonary Tuberculosis (in German). R. ISEBARTH* and O. WIEDEMANN. *Tuberkulosearzt*, February, 1960, 14: 144–162. (* Schlossgasse 68, Grenzach in Baden, Germany)

Cycloserine was given to 414 patients with "open" tuberculosis in 9 different hospitals; 199 of the patients had not received any prior treatment. The other 215 patients with chronic lesions had developed strains of tubercle bacilli resistant to isoniazid, streptomycin, and/or PAS. The results of this trial were highly encouraging. Roughly ½ of these patients had a follow-up period. Of 104 recent patients who had positive sputum at the beginning of treatment, 73 converted, but 19 of them became positive again during the follow-up period. Of 99 positive chronic cases, 38 became negative, and 16 of these had bacteriologic relapses.—J. HAAPANEN

Cycloserine–Isoniazid in the Treatment of Chronic, Resistant Pulmonary Tuberculosis. H. Lee*. *Dis Chest*, April, 1960, 37: 378–381. (* Piedmont Sanatorium, Burkeville, Virginia)

A small group of patients (46) who had received long-term chemotherapy and who represented failure of treatment with various combinations of streptomycin, PAS, and isoniazid by being resistant to all 3 drugs, with sputum consistently positive for tubercle bacilli, were treated with cycloserine and isoniazid. Bacteriologic conversion was prompt and reached a peak of 54 per cent in 6 months of therapy. Twenty-six per cent had relapses within a year or more after 12 months of therapy. Cavity closure occurred in 3 per cent, and moderate to marked roentgenographic improvement in 13 per cent. Treatment was discontinued in 3 per cent because of toxicity. The optimal duration of treatment with these 2 drugs would seem to be 6 months.—E. A. Rouff

Demethylchloretetracycline Therapy in Pneumonia, Scarlet Fever, and Other Infections. E. Lichter*, S. Sobel, H. Spies, M. Lepper, and H. Dowling. *AMA Arch Intern Med*, April, 1960, 105: 601–612. (* U. of Illinois, Chicago)

Demethylchloretetracycline, a new antimicrobial, is produced by a mutant strain of *Streptomyces aureofaciens*. This drug is more effective than its analogue, tetracycline, when equal amounts of both are tested against the common laboratory assay organisms *Bacillus aereus #5*, *Streptococcus 98*, or *Staphylococcus 209P*. In addition, many strains of *Staphylococcus aureus* organisms isolated from infected patients share this increased susceptibility. Of 29 patients treated for pneumococcal infections, 27 had pneumonia and 2 had an acute pneumococcal exacerbation of chronic bronchitis, 1 of these occurring in a patient with multiple myeloma. One patient had a pleural effusion. Fifteen of the patients with pneumonia gave prompt responses to therapy. In the group of 13 patients with delayed response exceeding 72 hours, 3 had developed pleural effusion before the beginning of therapy, 4 were preterminal and died from underlying neoplastic disease 8, 10, 10, and 20 days, respectively, after admission, in spite of successful treatment for pneumococcal pneumonia. The remaining 6 patients were afebrile on the 4th, 4th, 5th, 5th, 6th, and 9th days after admission, respectively. Both of the patients with chronic bronchitis became afebrile on the 4th day after therapy. In none of the patients was evidence of hemopoietic, hepatic, or renal toxicity apparent. Symptoms of gastrointestinal irritation were the only untoward reactions that could be attributed to the antimicrobial. It is apparent that these symptoms were related to the amount of the drug taken.
—T. H. Noehren

Additional Clinical Contribution to the Therapy of Pulmonary Tuberculosis by the Use of Small Intradermal Doses of Isoniazid (in Italian). P. Guglielmetti* and S. Sbragia. *Riv Pat Clin Tuberc*, No. 3, 1959, 32: 352–367. (* Ospedale Sanatoriale of INPS "G Banti," Pratolino (Firenze), Italy)

A report is given on 17 patients with recent pulmonary tuberculosis who were treated with small intradermal doses of isoniazid (40 mg. daily). The favorable results obtained with this therapy are reported.—G. Castelnuovo

Further Studies on the Appearance of Gynecomastia in Patients with Pulmonary Tuberculosis during Isoniazid Treatment (in Italian). C. Borsella* and B. Merelli. *Riv Pat Clin Tuberc*, No. 2, 1959, 32: 203–214. (* Sanat. Belfiore, Mantova, Italy)

This is the second paper presented by the authors on the appearance of gynecomastia during isoniazid treatment. Two new cases of gynecomastia are presented. The various clinical analyses, such as determinations of hormones in the urine, blood analyses, various liver tests, the histologic picture of the mammary glands, et cetera, seem to confirm that the mammary hypertrophy must be ascribed to an increased activity of the genitocortical area of the adrenals under the stimulus of isoniazid. The altered adrenal function is manifested by the change produced in the androgen/estrogen ratio, with an increase of estrogens from the enhanced excretion of pregnanediol in the urine, and by further increase of the estrogens and of the 17-ketosteroids after corticostropin administration.
—G. Castelnuovo

Pulmonary Tuberculosis Treated with High Doses of INH plus Glutamic Acid. F. Segarra* and D. Sherman. *Dis Chest*, April, 1960, 37: 382–389. (* Boston Sanatorium, Mattapan, Mass.)

There is some indication that the optimal dose of isoniazid has not been determined. The generally accepted daily dosage has been 3 to 8 mg. per kg. of body weight. Clinical and animal experimentation has indicated that higher dosages may be of correspondingly greater benefit. The toxicity (central nervous system) of isoniazid is lessened by the simultaneous administration of glutamic acid (Glutazide®) at a rate of 10 mg. for each 1 mg. of isoniazid. Patients on a high dosage of isoniazid (20 mg. per kg. of body weight) pre-

sented a remarkable improvement of appetite, weight, and feeling of well-being. During the short period of this therapy, no particular change relating to the treatment could be detected by roentgenographic or laboratory studies. Untoward side effects to the high isoniazid dosage were reduced by half in those also taking glutamic acid. —E. A. ROUFF

Kanamycin in the Surgical Treatment of Pulmonary Tuberculosis (in Japanese). T. HAGA*, K. ONO, T. ASANO, K. YOSHIMURA, S. WATANABE, K. TAZIMA, R. YONEDA, R. KOGA, and R. KOZI. *Jap J Thor Surg*, April, 1960, 13: 278–289. (* National Tokyo Sanatorium, Kiyose, Japan)

Kanamycin was given to 84 patients with streptomycin-resistant tubercle bacilli (54 cases) and streptomycin-susceptible bacilli (30 cases) when they underwent surgery. Of the 54 patients with streptomycin-resistant bacilli, 38 had "clean" pulmonary diseases (free of bronchopleural fistula or empyema), and 3 of them developed postoperative complications; 16 patients had "unclean" pulmonary diseases, and 1 of them developed empyema following surgery. Sputum became negative for tubercle bacilli after surgery, except in 15 patients in whom the bacilli were cultured only once in 5 cases; the source of bacilli was in the contralateral lung or due to complication in the remaining cases. Of the 16 patients with streptomycin-susceptible or no bacilli in the sputum before operation, none developed complications irrespective of the type of their pulmonary lesions. The sputum became negative in all of these cases. All of the 70 cases underwent lobectomy or pneumonectomy. Of the remaining 14 cases operated on for bronchopleural fistula or empyema, administration of kanamycin was generally effective, although some patients developed transient postoperative complication. It was concluded that the use of kanamycin in the above-mentioned conditions was usually beneficial as compared with other antimicrobials. —I. TATENO

Studies on the Resistance of Tubercle Bacilli to Kanamycin. IV. *In Vivo* Studies on the Cross Resistance of Tubercle Bacilli to Kanamycin, Fradiomycin, and Viomycin (in Japanese). T. MAEDA*. *Kekkaku*, April 1960, 35: 237–241. (* National Institute of Health, Tokyo, Japan)

The authors studied the therapeutic effects of kanamycin, fradiomycin (neomycin), and viomycin in guinea pigs infected intravenously with the H37Rv strain of tubercle bacilli resistant either to 1,000γ of kanamycin or fradiomycin per ml. Preliminary *in vitro* tests showed that these 2 drug-resistant strains had complete cross resistance to each of the other antimicrobials. Animal experiments revealed that kanamycin was ineffective in the animals infected with fradiomycin-resistant tubercle bacilli, and vice versa. However, viomycin was, to some extent, effective against the infection with both kanamycin- or fradiomycin-resistant tubercle bacilli.—I. TATENO

Treatment of Pulmonary Tuberculosis with Intravenous PAS–Streptomycin Pantothenate Infusions (in German). E. KUNTZ*. *Beitr Klin Tuberk*, October, 1959, 121: 269–292. (* Medizinische Klinik der Universität, Giessen a. d. Lahn, Germany)

Infusions of PAS-SP were given for about 3 months to 120 tuberculous patients. All of the 54 patients with acute exudative disease improved: the cavities closed or decreased considerably in size. Of 38 patients with positive acid-fast bacillary findings, 34 became negative. Roentgenographic improvement was noted in 44 of 47 patients with previously treated tuberculosis of long standing. Of 34 patients with positive acid-fast bacillary findings, 20 converted. The method is considered as initial treatment to be followed by other forms of therapy. Indications include acute, exudative cavitary processes, tuberculous meningitis, urogenital and skeletal tuberculosis, as well as the mixed forms of reactivated pulmonary tuberculosis.—Z. VIRÁGH

Studies on Penicillin Susceptibility of *Mycobacterium Tuberculosis* in a Liquid Culture Medium (in German). H. OEHRING*. *Tuberkulosearzt*, February, 1960, 14: 74–79. (*Semmelweissstrasse 4, Jena, Germany)

Susceptibility to several antituberculosis drugs and to penicillin was determined in 108 strains of *M. tuberculosis*. Five strains proved susceptible to 1 unit of penicillin per ml. Penicillin concentrations of 500–50,000 μ per ml. inhibited the growth of 81.5 per cent of the strains. A correlation could be established between susceptibility to penicillin on the one hand, and susceptibility to streptomycin, PAS, and isoniazid on the other. The addition of penicillin to the culture medium to inhibit the growth of contaminating bacteria is therefore inadvisable, as even small quantities of this antimicrobial may interfere with the growth of some strains of tubercle bacilli. —J. HAAPANEN

Sulfoniazide in Pulmonary Tuberculosis (in Italian). L. ABATE* and L. SPIGA. *Riv Pat Clin Tuberc*, No. 3, 1959, 32: 374–385. (*Ist. C.A. Pizzardi, Bologna, Italy)

A report is presented on 40 patients who had long-term pulmonary tuberculosis and who had been treated with sulfoniazide. In some cases some slight disturbances from intolerance to the drug and some hepatic troubles were observed but, in 50 per cent of the cases, good clinical results were obtained. In some patients the clinical improvement was accompanied by a corresponding roentgenographic improvement: the cavities were reduced and the exudates disappeared. —G. CASTELNUOVO

Attempt at Schematization of Treatment of Serofibrinous Pleurisy. (A Study of 300 Cases) (in French). A. MOREAU*, P. BOISSELIER, LEDEDENTE, and P. JARNIOU. *Rev Tuberc (Par)*, December, 1959, 23: 1137–1156. (*Paris, France)

Three groups of 100 young adults with tuberculous serofibrinous pleurisy were treated, respectively, with symptomatic therapy, antituberculous drugs, and antituberculous drugs plus steroid therapy. Comparison of the results revealed that antituberculous medication and steroids had a very definite effect on the temperature curve and sedimentation rate; antituberculous drugs did not modify roentgenographic clearing as significantly as did symptomatic therapy; however, resolution was markedly accelerated by steroids. Steroid therapy is indicated in pleurisy with acute or hyperacute onset which is diagnosed before the tenth day of illness. Steroids are given for 35 days, starting with 40 mg. of prednisone (Meticorten®), and the dose is decreased by 5 mg. every 5 days in association with 40 mg. of corticotropin every week. If steroids are started at a later stage, they do not prevent the development of pleural sequelae.—V. LEITES

The Medical Letter*. (*136 East 57 St., N.Y., N.Y.)

June 24, 1960, 2: 49–52: Spironolactone (Aldactone®) as a diuretic agent. Final review of vasopressors in treatment of shock: mephentermine (Wyamine®), methamphetamine (Methedrine®), methoxamine (Vasoxyl®), phenylephrine (Neo-Synephrine®), and epinephrine. The powdered food product "formula diet," Metrecal®. Index to Vol. 2, No. 1–12.

July 8, 1960, 2: 53–56: Paromomycin (Humatin®), the new oral antimicrobial derived from a strain of Streptomyces. New and old ergotamine drugs for migraine. Corticotropin (ACTH) versus corticosteroids.

PULMONARY PHYSIOLOGY

The Oxyhemoglobin Dissociation Curve in Anemia. T. RODMAN*, H. CLOSE, and M. PURCELL. *Ann Intern Med*, February, 1960, 52: 295–309. (*V.A. Hosp., Philadelphia, Penn.)

The affinity of hemoglobin for oxygen was studied in 23 anemic patients with normal, adult-type hemoglobin. The *in vivo* oxyhemoglobin dissociation curve of each patient was outlined by determining the oxygen tension, oxygen saturation, and pH of blood while the patient breathed different concentrations of oxygen. A reduction in the affinity of hemoglobin for oxygen in the form of a rightward displacement of the dissociation curve was demonstrated in patients with hemoglobin levels below 9 gm. per 100 ml. The displacement was moderate in patients with hemoglobin levels between 6.5 and 9.0 gm. per 100 ml., and more marked in those with less than 6.5 gm. per 100 ml. The dissociation curve had shifted back toward its normal position in those patients with severe anemia who were restudied after their hemoglobin content had been raised. The implications of a reduction in the affinity of hemoglobin for oxygen in the presence of anemia are discussed. It is concluded that the change is a desirable one because it facilitates the extraction of oxygen from the hemoglobin by the tissues (after authors' summary).—T. H. NOEHREN

Negative Pressure Breathing. M. BADER* and R. BADER. *Amer J Med*, March, 1960, 28: 333–336. (*Mount Sinai Hosp., N. Y., N. Y.)

Many gaps remain in our knowledge of the alterations in physiologic activities under the influence of negative pressure breathing. Since newer respiratory apparatuses are being constructed in which a negative pressure phase is incorporated, it becomes increasingly important from a practical standpoint to learn more about the cardiorespiratory and other effects of negative pressure breathing. Perhaps from such studies, additional information—as significant as the discovery of the left atrial stretch receptors—may be garnered. The area of greatest interest in connection with negative pressure breathing is concerned with renal function and the excretion of water. With continuous negative pressure breathing there is a significant diuresis. This diuresis is not accompanied by any significant change in renal hemodynamics, and there is little or no change in electrolyte excretion; indeed, significant natriuresis does not occur during negative pressure breathing even in individuals predisposed to sodium loss. The diuresis observed with negative pressure breathing is primarily due to increased

free water clearance. There is no significant change in osmolar concentration of the plasma or in the peripheral venous hematocrit. The diuresis is inhibited by the administration of antidiuretic hormones. It appears that negative pressure breathing produces a diuresis via a neurohormonal mechanism. This is initiated by stretch receptors located in the left atrium or at the ostia of the pulmonary veins, with impulses via afferent fibers in the vagus, leading through some undefined path to inhibition of the secretion of antidiuretic hormones.—T. H. NOEHREN

The Work of Breathing Through the Nose. J. BUTLER*. *Clin Sci*, 1960, 19: 55–62. (*U. of Pennsylvania, Philadelphia)

The nasal resistance ot 10 normal subjects was studied by airway-resistance measurements in the body plathysmograph and by posterior rhinometry. The work of mouth and of nose breathing was measured from pressure-volume diagrams. There was a large variation in the nasal resistance of different subjects and in individuals studied at different times. Nasal resistance averaged 1½ times the resistance of the lower airway. The work of lung movement at a rate of 20 breaths per minute with a tidal volume of 0.5 L. was more than doubled by breathing through the nose. Calculations of frictional work from values of nasal resistance obtained by posterior rhinometry showed fair agreement with measurements of the frictional work of nose breathing from the pressure-volume diagrams. Posterior rhinometry is a simple method of getting an approximate value of the resistance and work during nose breathing (Author's summary).—H. J. SIMON

Measurement of Carbon Monoxide Diffusing Capacity by the Single-Breath Method in Normal Subjects (in Japanese). H. KANAGAMI*, T. KATSURA, K. SHIRAISHI, K. BABA, and K. AONUMA. *Resp Circ*, April, 1960, 8: 387–391. (*Kosankin Kenkyujo, Tohoku U., Sendai, Japan)

The writers measured the carbon monoxide diffusing capacity (Dco) in 38 normal Japanese subjects in an attempt to obtain regression equations useful for the Japanese, who are smaller than the Caucasians. They found that the Dco was highly correlated with body surface area (BSA) ($r = +0.886$), body weight ($r = +0.767$), height ($r = +0.724$), and age ($r = -0.678$). The following regression equations were found useful: (*1*) Dco = 50.3 × BSA (in m^2) − 46.9, or, (*2*) Dco = (26.55 − 0.25 × age) × BSA (in m^2). A comparison was made between the predicted values of Dco calculated from equation (*1*) and those from equation (*2*), and good correlation was found. The writers recommend the first equation for clinical use because of the simplicity of calculation of the predicted values, provided that the BSA is between 1.23 to 1.81 m^2.—I. TATENO

The Ventilatory Response to Carbon Dioxide in Mitral Disease. H. G. PAULI*, F. E. NOE, and E. O. COATES. *Brit Heart J*, April, 1960, 22: 255–258. (*U. of Berne, Switzerland)

The regulation of ventilation in 7 patients with pure or predominant rheumatic mitral stenosis was investigated by measuring respiratory response to increasing CO_2 content of the inspired gases. Respiratory responsiveness, as defined by increase in specific ventilation produced by a given increase in arterial CO_2 tension, was found to be significantly lowered in comparison with that in 11 normal subjects. The extrapolated central threshold value for the arterial CO_2 tension was diminished in these patients, resulting in a slight rise of ventilation at the level of resting arterial PCO_2.—J. LORBER

A Study of the Mechanism of the Occurrence of Cerebrovascular Insufficiency in Senile Patients with Pulmonary Emphysema (in Japanese). M. MIYAZAKI*. *Resp Circ*, April, 1960, 8: 314–321. (*Osaka U., Japan)

The writer studied the correlation between the ventilatory pulmonary function, composition of blood, cerebral circulation, severity of retinal arteriosclerosis, and renal function, and the cerebral symptoms such as headache, dizziness, et cetera, in senile patients with pulmonary emphysema. It was shown that not only cerebral arteriosclerosis and anoxemia, but also functional spasm of cerebral blood vessels due to pulmonary dysfunction, were regarded as the factors leading to the occurrence of cerebral symptoms in these patients. It was also indicated that these phenomena were apt to occur in primary chronic pulmonary emphysema as well as in senile pulmonary emphysema. In connection with these findings, pathophysiologic studies indicated that when the senile patients who had severe pulmonary emphysema with cerebrosclerosis, coronary insufficiency, systemic metabolic disorders, et cetera, had complications of acute pulmonary diseases such as pneumonia, then cerebrovascular insufficiency was liable to occur after the development of anoxemia, respiratory acidosis, and cardiac insufficiency. It was proposed that cerebral symptoms which were thought to occur as a result of pulmonary dysfunction should be called "pulmonary encephalopathy," and that cerebrovascular insufficiency in which pulmonary dysfunction was thought to be the primary cause should be called

"pulmonary cerebrovascular insufficiency" or "cardiopulmocerebral apoplexy"; and, therefore, that these cerebral symptoms due to pulmonary dysfunction should be distinguished from other cerebral symptoms or cerebrovascular insufficiencies due to factors other than pulmonary dysfunction.—I. TATENO

Hyperventilation and Arterial Hypoxemia in Cirrhosis of the Liver. H. HEINEMANN*, C. EMIRGIL, and J. MIJNSSEN. *Amer J Med*, February, 1960, 28: 239–246. (*Columbia U., New York, N. Y.)

This study was undertaken to establish the coincidence of hyperventilation and hypoxemia in cirrhosis of the liver. The results show that hyperventilation, compensated respiratory alkalosis, and low arterial oxygen tension do occur concurrently in patients with cirrhosis of the liver. The low oxygen tension seems to be best explained by increased venous admixture, conceivably via vascular communications by-passing the alveolar-capillary bed. The mechanism maintaining hyperventilation remains obscure.—T. H. NOEHREN

A Study of Etiologic Factors in So-Called Primary Pulmonary Hypertension. A. RAWSON* and H. WOSKE. *AMA Arch Intern Med*, February, 1960, 105: 233–243. (*U. of Pennsylvania School of Med., Philadelphia)

Four patients with so-called primary pulmonary hypertension (PPH) were studied clinically and at autopsy. The histologic appearance of the lungs was similar in all cases, consisting essentially of marked intimal cellular proliferation in the small muscular arteries and arterioles, with severe vascular stenosis. Two patients had arthritis and Raynaud's phenomena. One patient had extrapulmonary lesions suggestive of a "collagen" disease. Two patients had close relatives with arthritis and Raynaud's phenomena. A review of well-documented published cases shows a higher-than-normal incidence of arthritis (8 per cent), Raynaud's phenomena (21 per cent), and lesions suggestive of "collagen" disease (10 per cent) in patients with PPH. It is suggested that many if not most cases of PPH may be related to the "collagen" group of diseases (after authors' summary).—T. H. NOEHREN

Studies of Pulmonary Function. B. G. FERRIS, JR*. *New Engl J Med*, March 17 and March 24, 1960, 262: 557–562, and 610–614. (*Harvard School of Public Health, Boston, Mass.)

This is a review of recent studies of pulmonary function. The topics discussed are: lung volumes, mechanical properties of the lungs, ventilatory tests, and gas exchange.—M. J. SMALL

Physiologic Dead Space in the Hamman-Rich Syndrome. R. HOLLAND*. *Amer J Med*, January, 1960, 28: 61–68. (*U. of Sydney, New South Wales, Australia)

Physiologic dead space has been measured in 5 cases of the Hamman-Rich syndrome, using arterial carbon dioxide tension for alveolar carbon dioxide tension. At rest, physiologic dead space was increased in 3 cases, sometimes grossly. The dead-space/tidal-volume ratio was elevated in all of the cases. On exercise, physiologic dead space increased greatly; its ratio to tidal volume showed no appreciable change from the resting ratio and was excessive in all cases. The increase was too great to be accounted for by errors in the method or an artifact caused by venous admixture. It is attributed to the development of focal emphysema. Increase in dead space correlates well with, and is believed to account partially for, clinical severity. In this condition, the dead space is too high at rest and on exercise for one to obtain "alveolar air" by end-tidal sampling. Similarly, the assumption of a dead space is unjustified. The meaning of "physiologic dead space" is discussed. Attention is drawn to the fact that it must be defined in terms of blood gas and not alveolar gas tensions, since the term itself implies our inability to choose any sample of air as representative of alveolar air (after author's summary).
—T. H. NOEHREN

Effects of Histamine on Pulmonary Ventilation in Man. A. BOUHUYS*, R. JONSSEN, S. LICHTNECKERT, S.-E. LINDELL, C. LUNDGREN, G. LUNDIN, and T. R. RINGQUIST. *Clin Sci*, 1960, 19: 79–94. (*U. of Lund, Sweden)

The effect of histamine on the clearance of nitrogen from the lungs during oxygen breathing has been studied in normal and asthmatic subjects. The nitrogen clearance remained unaltered during intravenous infusion of histamine. Inhalation of histamine aerosol retarded the nitrogen clearance and eventually caused respiratory distress. Inhalation of epinephrine or an antihistaminic drug antagonized this effect of histamine. The asthmatic subjects were more sensitive to inhaled histamine than were the normals. Administration of hexamethonium bromide decreased their sensitivity to near-normal levels, which suggests that autonomic nervous structures in the bronchial walls of the asthmatic subjects are exceptionally sensitive to histamine. Hexamethonium had no effect on the histamine sensitivity of normal subjects. It is suggested that a functional disorder of the autonomic nervous structures in the bronchial walls may be of importance in the pathogenesis of bronchial asthma (Authors' summary).
—H. J. SIMON

The Treatment of Respiratory Acidosis with THAM. G. L. BRINKMAN*, D. G. REMP, E. O. COATES, JR., and E. M. PRIEST. *Amer J Med Sci*, March, 1960, 239: 341–346. (*Henry Ford Hosp., Detroit, Mich.)

The effect of Tris(hydroxymethyl)aminomethane (THAM) on 4 individuals with respiratory acidosis is recorded. Three of these patients had severe diffuse obstructive emphysema with arterial oxygen unsaturation and carbon dioxide retention; the fourth had carcinoma of the lung with hypoventilation resulting in respiratory acidosis. The usual therapeutic agents employed to counteract acidosis are the salts of weak organic acids, but THAM, in contrast, is a weak organic base which at a pH of 7.4 is 80 per cent dissociated. After administration of THAM there was a consistent rise in the arterial blood pH, a reduction in minute ventilation, and a considerable increase in urinary pH and urinary excretion of bicarbonate. A brief report is included on the 2 patients in whom this buffer has been used therapeutically.—W. J. STEININGER

The Effects of Natural Sleep and Hypersomnolent States on Respiratory Function. H. SIEKER*, A. HEYMAN, and R. BIRCHFIELD. *Ann Intern Med*, March, 1960, 52: 500–516. (*Duke Hosp., Durham, N. C.)

Natural sleep and the hypersomnolence of narcolepsy are associated with a depression in respiratory function which results in a slight decrease in arterial oxygen saturation, retention of carbon dioxide, and decreased sensitivity of the respiratory center to carbon dioxide stimulus. Patients with narcolepsy may also manifest obesity, Cheyne-Stokes respiration, polycythemia, and other signs of the hypoventilation–cardiopulmonary syndrome. It is suggested that some narcoleptic patients represent "formes frustes" of the Pickwickian syndrome, and that these two conditions, as well as certain instances of primary hypoventilation, have a common neurogenic factor (Authors' summary).
—T. H. NOEHREN

The Effect of a New Carbonic Anhydrase Inhibitor (Dichlorphenamide) in Respiratory Insufficiency. A. NAIMARK*, D. BRODOVSKY, and R. CHERNIACK. *Amer J Med*, March, 1960, 28: 368–375. (*Winnipeg General Hosp., Manitoba, Canada)

Dichlorphenamide, which has a capacity to inhibit carbonic anhydrase that is estimated to be 30 times that of acetazolamide, has recently been developed. It presumably differs from the latter agent in that it is capable of producing a chloruresis so that metabolic acidosis is less likely to occur. This paper reports the effects of dichlorphenamide therapy in 15 patients with chronic respiratory insufficiency. All but 1 showed clinical improvement. In most cases, marked improvement in arterial blood gas tension was associated with an increased alveolar ventilation. This improvement has been sustained during prolonged administration of the drug. Possible mechanisms of action of this drug have been investigated and are discussed.—T. H. NOEHREN

Ventilation and Acid-Base Balance in Healthy Persons during Heavy Exercise; Examinations with the Metabograph of Fleisch with Continuous Analysis of Arterial Gases (in German). TH. ABELIN* and M. SCHERRER. *Schweiz Med Wschr*, March 26, 1960, 90: 369–374. (*Universitäts-Klinik, Bern, Switzerland)

Treadmill exercise tests were performed on 7 healthy male students, 22 to 26 years old. The constant work load was from 100 to 260 watts. With Fleisch's metabograph, ventilatory minute volume, oxygen consumption, and carbon dioxide elimination were continuously registered. Arterial blood samples were withdrawn every 2 minutes. A chemical steady state was observed only at loads of 100 to 140 watts. With additional loading, a metabolic acidosis regularly set in, although ventilation remained at a constant level within the normal oscillations, simulating a respiratory steady state. A relative hyperventilation was present at all work loads above 140 watts. This hyperventilation seemed to be strictly related to the degree of metabolic acidosis. It may be concluded that, at the lower level, characterized by a minimal ventilatory equivalent for oxygen, the critical partial pressure of oxygen of about 5 mm. Hg. was realized in muscular tissue. Below this level, aerobic carbohydrate metabolism is impossible. At heavier loads a metabolic acidosis was observed, which was not fully compensated by ventilation. Arterial CO_2 tension and pH decreased to very low values, while O_2 saturation generally remained at high levels. The limiting factor for muscular work in healthy young subjects seems to be insufficient muscular blood perfusion.—J. HAAPANEN

MICROBIOLOGY AND IMMUNOLOGY

Identifying Acid-fast Bacilli by Their Niacin Production (in Finnish). O. MÄKELÄ* and P. MÄKELÄ. *Duodecim*, February, 1960, 76: 151–155. (*Serobakteriologinen Laitos, Helsinki,

Finland)

Konno's niacin test was positive in all of 117 strains of human tubercle bacilli that were cultivated in Kirchner's liquid medium. All of the other strains (3 of *M. bovis*, 2 of *M. avium*, and 12 nonpathogenic: BCG, *M. phlei*, et cetera) gave negative results. Bacteria grown on solid medium gave a smaller number of positive results.
—J. Haapanen

A New Method for the Differentiation of Bovine Tubercle Bacilli from Other Types by Means of Nicotinamidase Reaction. Report I (in Japanese). K. Konno* and H. Nagayama. *Kekkaku*, April, 1960, 35: 287–291. (*Kosankin Institute, Sendai, Japan)

Qualitative and quantitative analyses were made of the nicotinamidase activity of cell-free extracts of different types of mycobacteria. Only the bovine tubercle bacilli, irrespective of their virulence and isoniazid susceptibility, revealed remarkably lower nicotinamidase activity than did other types of mycobacteria. The bovine bacilli hydrolyzed and produced only 0.1 micromole of ammonia from 10 micromoles of nicotinamide, whereas human, avian, and paratubercle bacilli produced more than 3 micromoles, and nonpathogenic acid-fast bacilli produced more than 6 micromoles of ammonia. Qualitative tests without distillation of ammonia from the mixture of nicotinamide and extracts of mycobacteria also showed negative reactions for bovine tubercle bacilli and positive reactions for other types of mycobacteria. The writers conclude that bovine tubercle bacilli can be biochemically distinguished from other types by determining the nicotinamidase activity of cell-free extracts of the bacteria.
—I. Tateno

Pathogenic Acid-fast Mycobacteria (in Spanish). L. F. Bojalil*. *Rev Lat Amer Microbiol*, Supplement No. 2, December, 1958. (*Escuela de Medicina, México 7, D. F.)

The morphology, cultivability, biochemical properties, resistance to physical agents, susceptibility to antimicrobials, pathogenicity to animals, *in vitro* virulence, et cetera, are described of *M. fortuitum Cruz*, 1938; *M. ulcerans* McCallum *et al.*, 1948; *M. balnei* Nörden and Linell, 1951; the 4 different types of mycobacteria classified by Runyon; *Nocardia intracellularis* Cuttino and McCabe, 1949; *M. abscessus* Moore and Fredrick, 1953; the Mycobacterium isolated by Van der Hoeven in 1938, as well as the 3 classic types (human, bovine, and avian) of *M. tuberculosis*.
—Z. Virágh

EXPERIMENTAL PATHOLOGY

The Results of the Experimental Use of Sulfur Dioxide in the Production of Material for Cell Studies in Lung Cancer. W. Allan* and P. Whittlesey. *Ann Intern Med*, February, 1960, 52: 326–329. (*Johns Hopkins U. School of Med., Baltimore, Md.)

The use of sulfur dioxide in the nebulized form is an efficacious method for producing bronchial secretions in patients who have pulmonary lesions without cough or sputum. The authors have not encountered any serious deleterious side effects from its use. It is almost universally effective in cough and sputum production. The simplicity of the procedure opens up avenues of approach in the survey of individuals in industry and may lead to its application in clinics and office practice, much as the vaginal smear is now employed.

The authors examined 229 patients who had neither cough nor sputum, and the sulfur dioxide exposure resulted in the production of cough and secretions in 226 of this group. There were 3 failures; none of the 3 had cancer of the lung. Of this group, 63 patients had proved cancer of the lung either by node biopsy or thoracotomy with biopsy, or by removal of lung tissue. Of the 63, there were 62 positive cell studies. The 1 instance of a negative cell study was in a patient who had an encapsulated necrotic lesion (adenocarcinoma) at the apex of the right lung. Though this is a numerically small group, the percentage of positive reactors was 98.4 per cent. In another group of 14 patients with coin lesions without cough or sputum, sulfur dioxide exposure resulted in the production of cough and sputum in all 14 cases. There were 5 positive cell studies for malignancy on direct examination of these lesions. A miscellaneous group of 107 patients without cough and sputum was studied. The results in this group have been entirely negative.
—T. H. Noehren

Further Studies with Serotonin and Experimental Pulmonary Embolism. B. Cobb* and E. M. Nanson. *Ann Surg*, April, 1960, 151: 501–506. (*U. of Saskatchewan, Saskatoon, Canada)

Purified extract of serotonin, crude extract of serotonin from fresh blood clots, and multiple small fresh blood clots all produce in the dog a similar picture of pulmonary hypertension, peripheral hypotension, hyperpnea, bradycardia, and defecation. Heparin in clinical doses exerts a protective effect in dogs to infusion of serotonin and to multiple small fresh blood clots in 94 per cent. It is recommended that intravenous heparin in 5,000-unit doses be given as an emergency

measure in pulmonary embolism. This should antagonize any further release of serotonin and diminish the adverse systemic effects of the pulmonary embolism.—M. J. SMALL

Behavior in the Circulation of the Radioactive Pulmonary Embolus and Its Application to the Study of Fibrinolytic Enzymes. M. HUME*, W. W. L. GLENN, and T. GRILLO. *Ann Surg*, April, 1960, 151: 507–516. (*Yale U. School of Med., New Haven, Conn.)

It has been shown that clots injected into the venous circulation decline in mass steadily until, by 4 weeks, very little if any of the original clot remains. Observation of the radioactive embolus confirms previous demonstration of spontaneous clot lysis and supplies additional information on the rate of clot removal. There is also suggestive evidence that new thrombus may be deposited even as the mass of the experimental clot is being reduced in the circulation. Weighing the clot permits a somewhat more precise estimate of the rate of change in clot mass, and has aided the evaluation of several details which bear upon the stability of the clot in the circulation. Identical clots that could serve as an external control have been used and it has been observed that, if the weight of these clots is well maintained *in vitro*, the clot in the circulation also demonstrates an acceptable stability. Observation of these control clots, when compared with the experimental embolus, is of some value as an indication of clot lysis in those experiments in which fibrinolytic enzymes were used, but even more reliance can be placed upon a demonstration of changes in radioactivity occurring after a steady baseline has been reached. The failure to demonstrate complete lysis in these experiments indicated the complexity of this new therapeutic field. It is anticipated that subsequent experience will show how crude an attempt to effect lysis is represented by the introduction of a simple excess of a potent lytic agent or activator.—M. J. SMALL

Collection of Sputum for Cytologic Examination: Spontaneous vs. Artificially Produced Sputum. W. O. UMIKER*, D. R. KORST, R. P. COLE, and S. G. MANIKAS. *New Engl J Med*, March 17, 1960, 262: 565–566. (*V. A. Hosp., Ann Arbor, Mich.)

This study compares the effectiveness of multiple spontaneous cough specimens with sputum artificially obtained by the aerosol technique. From 145 persons who were suspected of having lung cancer, and who were being investigated cytologically, 2 groups were selected for artificial induction of sputum. The first consisted of 17 patients who had no cough, unproductive cough, or spontaneous sputum that did not contain pulmonary histiocytes. The second group was composed of 21 patients who had "satisfactory" spontaneous sputum that did not contain cancer cells. In 32 patients the diagnosis of cancer of the respiratory tract was subsequently established by histologic examination, including 10 patients in the selected groups. Sputum was produced by the saline-aerosol technique of Bickerman *et al.*

The first spontaneous sputum sample was adequate in only 60 per cent of the 145 patients. The second attempt was often more rewarding and, when 3 specimens were collected, the percentage of patients with at least 1 satisfactory specimen increased to more than 90 per cent. Excellent sputum specimens were obtained by means of heated saline-aerosol inhalation from the 17 patients who had no cough, or whose spontaneous sputum was unsatisfactory for cytologic examination. The potential value of this procedure in the detection of lung cancer in screening asymptomatic subjects is apparent. The application of this simple technique increased the rate of positive cytologic diagnoses of cancer of the respiratory tract from 68.8 per cent to 87.5 per cent in the group of 32 histologically proved cases; 31 (96.9 per cent) of the 32 patients had positive or suspicious smears.—M. J. SMALL

Enzymatic Determination of *in Vitro* Lysis of Leukocytes by Tuberculin. B. W. JANICKI* and R. A. PATNODE. *Proc Soc Exp Biol Med*, November, 1959, 102: 311–314. (*V. A. Hosp., Washington, D. C.)

Guinea pigs were sensitized to tuberculin by the injection of heat-killed *M. tuberculosis* H37Rv. The leukocytes obtained from the animals were lysed in the presence of PPD *in vitro*. The degree of lysis was estimated by a lysozyme assay method. This method was found to be an acceptable substitute for microscopic cell counts in *in vitro* lysis of leukocytes by tuberculin.
—E. S. LEAKE

Failure to Transfer Delayed Tuberculin Sensitivity from Human to Animal Species. F. T. RAPAPORT* and J. W. MILLAR. *Proc Soc Exp Biol Med*, December, 1959, 102: 714–717. (*New York U., N. Y., N. Y.)

Peripheral blood leukocytes obtained from strongly tuberculin-sensitive human donors were given to monkeys and rabbits by various routes. The recipients were skin tested periodically up to 5 weeks following cell transfer. Neither test nor control animals developed tuberculin sensitivity during this period.—E. S. LEAKE

An Antituberculous Diffusing Vaccine (V.D.S.): Its Biologic Characteristics and the Length of Time of Its Activity (in Italian). M. Bacchiega* and G. Vitale. *Riv Pat Clin Tuberc*, No. 3, 1959, 32: 295–330. (*Centro Vaccinogeno Antitubercolare, Bologna, Italy)

This vaccine is an antituberculous vaccine prepared with killed tubercle bacilli to which hyaluronidase is added. Its use, the methods for its preparation, its characteristics, and its action in guinea pigs are described in detail. Moreover, in order to evaluate the persistence of the activity of such a vaccine over a period of time, various pools of this vaccine prepared at different periods (from 6 months to 7½ years) have been tested in guinea pigs. All of these preparations produced a remarkable specific immunity in guinea pigs, confirming that this vaccine is able to maintain unaltered in activity and innocuousness for a long period of time.—G. Castelnuovo

PUBLIC HEALTH AND EPIDEMIOLOGY

A Limited Survey of Radiation Exposure from Medical Fluoroscopes. R. O. Gorson*, J. Lieberman, and M. Green. *Radiology*, December, 1959, 73: 898–910. (*Jefferson Med. College Hosp., Philadelphia, Penn.)

In the Philadelphia area, a survey was made of the radiation characteristics and manner of use of 22 fluoroscopes owned by 8 hospitals and 4 city clinics, and 59 fluoroscopes in the offices of private physicians. Only 2 fluoroscopes met all of the design and performance recommendations of *Handbook 60* of the National Bureau of Standards. About 7 per cent of the units were judged satisfactory by proposed performance standards. However, almost half of the units produced an exposure dose rate of less than 10 r per minute at the panel surface under normal conditions of use, and were not considered unduly hazardous. Fluoroscopes used by hospitals and roentgenologists produced radiation at lower average exposure levels (8.9 r per minute) and higher half-value layer (2.9 mm. of aluminum) than those used by nonroentgenologists (16.3 r per minute and 1.9 mm. of aluminum). Fluoroscopes owned by hospitals and roentgenologists were operated at lower average milliamperage (ma) (3.3) settings and higher peak kilovoltage (kvp) (79) settings than those used by nonroentgenologists (4.7 ma and 66 kvp). Although many fluoroscopes produced unnecessary amounts of stray radiation, the average exposure of physicians in private practice appeared to be very low (5 mr per week to the right arm and 2 mr per week to the left shoulder) due to the low average work load (6.5 minutes per week). Most nonroentgenologists limit fluoroscopic examinations to the chest, and many of them recently have curtailed use of fluoroscopy. It is estimated that more than 90 per cent of the fluoroscopes could be made acceptable by one or more of the following modifications: adding more aluminum filtration, decreasing maximal ma setting, decreasing maximal shutter opening, and adding accessory shielding.—W. J. Steininger

Initial Photofluorographic Diagnoses and Their Practical Significance in a Survey of 6,647,583 Photofluorograms (in Swedish). S. Wijkström.* *Nord Med*, October 22, 1959, 62: 1537–1543. (*Medicinalstyrelsen, Stockholm 5, Sweden)

From 1946 through 1958, a total of 11,520 new cases of active intrathoracic tuberculosis was detected among 6,647,583 photofluorograms. The prognosis of these patients was better than that of patients whose tuberculosis was diagnosed by other means. Sarcoidosis was diagnosed 2,236 times, and tumors in 1,651 instances. There were more than 12,000 cases of cardiovascular disease. Due to the decreasing incidence of tuberculosis, it is proposed to arrange systematic surveys only among those groups in which the incidence of tuberculosis is higher than the average. A central archive where all the fluorograms could be collected would be of great help in further controls. —J. Haapanen

Serum Neuraminic Acid in Silicosis and Silicotuberculosis (in Italian). M. Finulli* and E. Ghislandi. *Med Lavoro*, November, 1959, 50: 683–687. (*U. of Milan, Italy)

The neuraminic acid content in the serum of 8 normal persons, 50 patients with silicosis, and 8 with silicotuberculosis was established by Boehm's method. It was found that the mean value of neuraminic acid in the normal persons was 60.2 mg. per 100 ml. of serum, 85 mg. in the silicotic patients, and 116 mg. in the patients with silicotuberculosis. The increase of this substance in silicosis apparently is due to the increase of serum mucoproteins; the increase observed in the patients with silicotuberculosis was certainly caused by an increase in the nonmucoprotein fraction of the neuraminic acid as well. —I. Archetti

Pulmonary Talcosis, a Clinical and Environmental Study. J. Messite*, G. Reddin, and M. Kleinfeld. *AMA Arch Industr Health*, November, 1959, 20: 408–413. (*Division of Industrial Hygiene, New York State Department of Labor, N. Y., N. Y.)

An industrial hygienic survey of the talc mines and mills in St. Lawrence County, New York, showed marked improvement in the engineering and medical control as compared to that found in the study conducted in 1940. Although the inci-

dence of pulmonary talcosis in the millers has not changed appreciably, the severity and progression of the disease have been diminished. The reduction in the dust exposure in the mines and the lower incidence of pulmonary fibrosis among the talc miners are primarily due to the institution of wet drilling. A comparative study of talc millers in two different regions of New York State showed that, while the degree of exposure to talc dust was similar, the incidence and severity of the talc pneumoconiosis was considerably less when the exposure was to the nonfibrous variety of talc. The data indicate that, while both types of talc can produce pulmonary fibrosis, the fibrous or tremolite variety is the more pathogenic (after authors' summary).—T. H. NOEHREN

Importance of Environmental Factors in the Epidemiology of Tuberculosis in Children (in Italian). L. SERAFINI*. *G Ital Tuberc*, September–October, 1959, 13: 287–381. (*Cl. Pediatrica, U. of Milan, Italy)

These data are based on observations that were made from 1949 to 1958 in the Pediatric Department of the University of Milan in 803 cases of tuberculosis in children. The frequency of the disease among all of the children was 3.88 per cent, and showed a tendency to decrease (irregularly, however). Tuberculosis caused at least 1/10 of the bronchopneumopathies and 32.14 per cent of the meningitis. Among the more commonly observed forms were pulmonary localization (33.50 per cent), tracheobronchial adenopathy (16 per cent), and meningitis (22.54 per cent). The decrease of meningitis and of miliary and exudative processes was irregular. The source of infection could be found in 35.86 per cent of the cases: in 95.80 per cent it was familial. The severity of the disease and the percentage of meningitis were higher in children whose source of infection could be established. It was not possible to find a greater incidence of tuberculosis in the children of poor classes, but the more severe cases were found among peasants. About 68 per cent of the children were ill in the first semester of the year; pleuritis and miliary tuberculosis were more frequent in the winter and spring periods.
—I. ARCHETTI

Infectivity of the Primary Tuberculous Complex. A. W. DICKIE* and R. D. G. CREERY. *Brit Med J*, December 26, 1959, No. 5164: 1453–1454. (*Royal Belfast Hosp. for Sick Children, Ireland)

Between 1953 and 1954, 103 actively tuberculous children were hospitalized on the general wards of the Belfast Hospital for Sick Children. The average length of hospitalization was 85 days. No attempts at isolation were carried out. Among 209 other children who were tuberculin negative and hospitalized at the same time for an average length of 58 days, it was possible to follow up 177, and at no time during the period of observation within the hospital or after discharge did any child develop a positive tuberculin reaction. The low infectivity of pulmonary tuberculosis in childhood is probably due to the small size of the primary foci, to their rapid healing, and to the child's habit of swallowing rather than spitting out his sputum.—E. A. RILEY

The Actual State of the Tuberculosis Problem in Czechoslovakia (in Czech). J. JEDLICKA*. *Cas Lek Cesk*, July 10, 1959, 98: 888–890. (*Charles U., Prague, Czechoslovakia)

As a result of modern antimicrobial therapy, the mortality of tuberculosis has decreased considerably, but the longer-living tuberculous patients are causing a great increase in morbidity. This morbidity increase is not only due to their longer life span, but is also due to the increasing number of sources of infection. The average age of people dying from tuberculosis has increased from 37 years in 1947 to 57½ years in 1957. The chronicity of the illness increased similarly at the same time. In 1947, the tuberculous disease of patients admitted to hospitals averaged a duration of 2½ years, while in 1957 it was of 7 years duration. The Czechoslovak antituberculosis campaign is based on regional institutes of health. Their tuberculosis departments have three different services: hospital, polyclinic, and hygienic-epidemiologic. The insufficient number of hospital beds for tuberculous patients is the most acute problem. According to the author's opinion, at least 5,000 to 6,000 new beds are necessary and, if they are not provided, the whole antituberculosis campaign will remain at a stand-still.
—J. ILAVSKY

Influence of Skin Testing on the Serologic Diagnosis of Tuberculosis and Histoplasmosis. D. C. HEINER*. *AMA J Dis Child*, November, 1959, 98: 673–674. (*U. of Arkansas, Little Rock)

Within the past year, reports in the literature have appeared which suggest the utility of precipitin reactions in agar gel in making the diagnoses of tuberculosis and histoplasmosis. One of the reports indicated that histoplasmin skin tests frequently stimulate the production of high titers of circulating antibodies in sensitized persons. The present study was undertaken to determine more fully the effects of tuberculin and histoplasmin skin tests on serum antibodies with the use of agar diffusion techniques. It was found that histoplasmin and tuberculin skin tests may in themselves cause the production of circulating

antibodies, particularly in persons with strongly positive intradermal reactions, thus requiring caution in the interpretation of serologic reports following skin tests. Antibodies due to skin testing have not been detected earlier than 5 days after an initial intradermal injection. Therefore, it is suggested that serum specimens for antibody studies should be drawn within 4 days of the time of a skin test, preferably at the time of the injection or when the reaction is read at 48 hours. —M. J. SMALL

Uncooperative Tuberculous Patients (in Spanish). C. EPIFANIO*. *Hoja Visiol*, June–September, 1959, 19: 93–104. (*Facultad de Medicina, Montevideo, Uruguay)

A study is reported of 340 (252 men and 58 women) unruly, "asocial," tuberculous patients who refused to cooperate with hospital personnel and left the institutions without regular discharge. A survey disclosed that the patients concerned were living in substandard environments in dwellings unworthy of the name, and had a high illiteracy rate; lack of working habits, alcoholism, and social vices were important prevalent factors. Normal and pathologic psychic alterations brought on by tuberculosis are discussed. All of the cases studied were evaluated and followed by a psychiatrist and a well-trained team of social workers. Each case was judged in accordance with psychologic and social backgrounds.—H. GARCIA

Follow-up of Tuberculous Recalcitrants. E. KUPKA* and D. L. GIBSON. *Public Health Rep*, January, 1960, 75: 21–25. (*California State Dept. of Public Health, Berkeley)

Between December, 1950, and December 31, 1956, 211 recalcitrant tuberculous patients were sentenced to a special California Medical Facility by court action. This procedure has proved practicable and useful. It not only decreased the hazard of transmission of disease, but also created an opportunity for the commencement or continuation of much needed treatment for the patients. Although the attitude of the majority of patients did not improve as a result of their incarceration, most of them remained under some type of medical supervision following discharge. However, many evaded regular medical supervision, especially after 1 year; 1 of 8 patients had to be readmitted to the State Facility; and a third of those subsequently admitted to local tuberculosis hospitals again resorted to unapproved self-discharge. Nevertheless, the data indicate that, by the time of the study, more than half of the patients had reached the classification of inactive or probably inactive. The majority of health jurisdictions in the State have sent at least 1 patient to the Facility, which would indicate that it is meeting a real need, but the small total (211 in 6 years) indicates that it is not being used indiscriminately or excessively.—E. DUNNER

A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India. TUBERCULOSIS CHEMOTHERAPY CENTER, INDIA*. *Tubercle*, December, 1959, 40: 468–476. (*Madras, India)

In India, as in most underdeveloped countries, the tuberculosis problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of tuberculosis in the country has been estimated at 2½ million, but only 23,000 beds are available for tuberculosis. In these circumstances, great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment in cases of pulmonary tuberculosis. The findings of the present study, based on a comparison of the 2 types of treatment over a period of 12 months, show that despite the manifest advantages of sanatorium care—rest, adequate diet, nursing, and supervised medicine-taking—the merits of domiciliary chemotherapy are comparable to those of sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established (Author's summary). —M. J. SMALL

Present Aspects of Primary Tuberculosis among Soldiers of the French Armed Forces in Germany. A Study of 122 Cases (in French). J. LE MELLETIER*, J. KLARNET, R. CHEVALIER, ZECCA, and MLLE. C. GRANGER. *Rev. tuberc. (Par)*, October–November, 1959, 23: 1001–1016. (*Paris-Wildbad, France)

Among the soldiers of the French Armed Forces in Germany, 63 per cent had negative tuberculin reactions on induction in 1957 and 1958. The incidence of negative reactors was higher among those from rural areas. Of the 122 cases of tuberculosis discovered less than 1 year after a negative tuberculin reaction was demonstrated, only 27 per cent had adenopathy visible on the roentgenogram; 46.6 per cent had pleural effusion; 30 per cent presented the picture of ordinary adult tuberculosis (infiltrations with or without cavitation and without tracheobronchial adenopathy). This form was more frequent in soldiers from urban areas, while tuberculous adenopathy and pleural effusion were more commonly seen among soldiers from rural areas. The sputum revealed *M. tuberculosis* in 44.2 per cent; in cases of pulmonary tuberculosis without adenopathy, the proportion was 86.5 per cent.—V. LEITES

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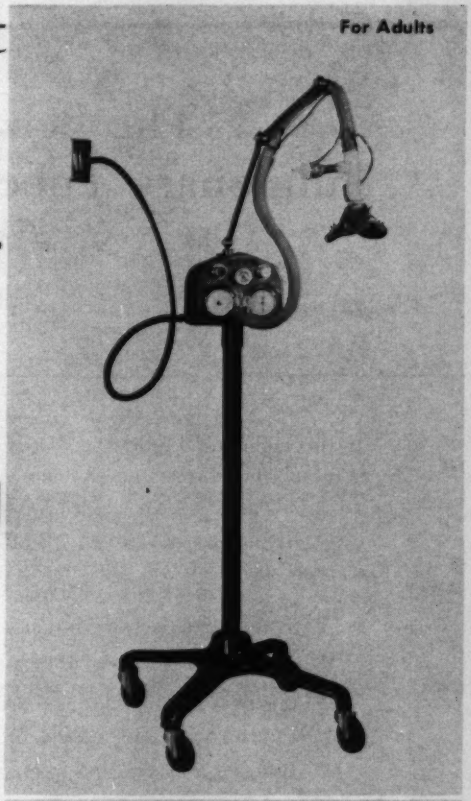

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